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ALLERGY—ITS DISTRIBUTION AND THE HEREDITARY CONCEPT

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I. Distribution of Allergy

WE collected data for purposes of comparison with previously published studies. In the course of establishing methods for the collection of our material, we discovered that varying criteria had been employed by different investigators in an attempt to evaluate the same problem.

The subjects in some studies were adults, in others children, and in still others both children and adults.

The extent of inquiry into the pedigrees varied. Comparisons had been drawn between pedigrees which included only direct antecedents and those which included both direct and collateral antecedents.

The interpretation of the allergic state was not uniform. On the one hand, certain investigators considered only hay fever, asthma, and urticaria as manifestations of the allergic state; others accepted as equivalents a variety of syndromes in the nasobronchial, cutaneous, gastrointestinal, ocular and genitourinary systems, as well as migraine and epilepsy. The exciting agent might be an inhalant, ingestant, drug, injectant, bacterium or even factors of a mechanical, physical, or psychological nature.

Conklin[16] points out that the value of statistics depends upon a proper classification of the things measured and enumerated. We shall describe in detail the collection of our data, present our findings, and then attempt to show how certain differences in criteria modify the inferences drawn.

COLLECTION OF DATA

The data for this study were obtained from an analysis of 250 allergic children and their families. The children ranged in age from infancy to sixteen years. These

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patients were seen chiefly in private practice, but some were clinic patients who met our need for intelligent and complete co-operation. The families were gathered in a large metropolitan area, and were all English-speaking.

Each history was taken by one of us (B.R.) to assure a certain degree of uniformity. Both the mother and the father of the patient were interrogated whenever possible. The family history was inquired into through at least three generations on both the maternal and paternal sides, including both direct and collateral antecedents. Where there was any doubt in the minds of the parents, we asked that the inquiry be pursued with other members of the family. We had the opportunity to check the information during subsequent visits when tests were being performed on the child; in this way dubious evidence was either corroborated or refuted. It is not out of place to digress for a moment to comment upon human nature and its influence on the accuracy of a history. Allergic afflictions seemed to be prevalent on the maternal side when the husband was questioned, and it was chiefly on the paternal side when the wife was interrogated. Faced with resentment which was not at all unique, one might be led to believe that one or the other side was riddled with allergy. We do feel, however, that the information gleaned after persistent questioning in the course of many visits presents to a fair degree the actual state of affairs.

In the first interview, we laid the groundwork for our inquiry by acquainting the parents with the manifestations which we regarded as allergic: namely, asthma, hay fever, eczema and recurrent urticaria. We included only eczemas of long duration that involved several parts of the body and that were differentiated from nonallergic dermatitis and such conditions as might result from parasitic infections. With urticaria, we did not regard as allergic a simple attack of hives, or even two or three isolated attacks; we noted as positive those cases only in which episodes were oft-repeated, the urticaria giant in character, involving the covered parts of the body, and associated with angioneurotic edema. We did not include migraine, gastrointestinal disturbances, or epilepsy as allergic manifestations unless closely related to other well-defined allergic disorders. With older antecedents, we had to differentiate cardiac asthma or some form of infectious bronchitis from true asthma. Naturally the less accessible the antecedent, the more unreliable the data.

The same criteria were applied to the patients themselves. For example, a child who seemed suggestively asthmatic gave a typical pertussis blood count that helped us to establish a proper diagnosis. In skin conditions particularly, a differential diagnosis is important; we have had cases referred to us with a diagnosis of eczema which were ruled out as scabies, impetigo, dermatitis venenata, trichophytosis, et cetera.

Of the 250 cases, 177 were studied completely. We had the unique opportunity of keeping the majority of these children under observation for a year or longer. A complete study included skin testing, blood chemistry, cytological studies, repeated eosinophil counts, Mantoux test, Dick test, Shick test, intracutaneous horse serum tests, x-rays and urinalysis. The skin tests were performed by J. E. G.* In each test survey, all available proteins were used and, in addition, extracts were made from environmental substances. When the significance of a test was doubtful, it was repeated on various parts of the body and the observations checked by B. R. In many instances, tests were completely repeated. The majority of the tests were done by the scratch method, but where it seemed indicated, intracutaneous testing was employed. Clinical tests were done in many instances, and, whenever possible, the presence of the Prausnitz-Küstner antibodies was determined. In twenty-one instances, patients gave no reactions to any of the skin tests; clinical observations and repeated evidence

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TABLE I. INCIDENCE OF POSITIVE ALLERGIC FAMILY HISTORIES IN 250 ALLERGIC PATIENTS AND 6,116 PATIENTS COLLECTED FROM THE LITERATURE

Source	Ref. No.	Year	Number of Cases	Positive Family Incidence	Adults or Children	Condition Studied
Salter	46	1882	217	39.0%	Both	Asthma
Cooke and Vander Veer	18	1916	504	48.5%	Both	Allergy
Adkinson	1	1920	400	48.0%	Adults	Asthma
Schloss	47	1920	80	58.7%	Children	Allergy
Coke	14	1923	350	46.0%	Both	Asthma
Spain and Cooke	52	1924	462	58.4%	Both	Asthma and Hay Fever
Comby	15	1925	75	58.0%	Children	Asthma
Rowe	44	1926	110	70.9%	Children	Asthma
Menagh	26	1927	300	40.0%	Both	Asthma
Balyeat	4	1927	100	73.0%	Children	Asthma
Rackemann	33	1927	1074	42.0%	Both	Asthma
Peshkin	31	1928	278	42.5%	Children	Asthma
Bullen	8	1929	500	38.6%	Both	Asthma
Balyeat	3	1930	1000	60.1%	Both	Asthma and Hay Fever
Bray	5	1931	200	68.5%	Children	Asthma
Rowe	45	1931	400	58.0%	Both	Asthma
Wiener, Zieve and Fries	59	1936	66	28.7%	Children	Allergy
Present Series		1951	250	54.4%	Children	Allergy

Total number of cases.....6,366
Total number positive family histories...3,302
Positive family incidence.....51.9%

TABLE II.

INCIDENCE OF POSITIVE FAMILY HISTORY IN NONALLERGIC AND ALLERGIC CASES, VIEWED FROM THE EXTENT OF ANTECEDENT PEDIGREE INQUIRED INTO

Source	Type of Case	No. of Cases	Extent of Antecedent Pedigree Inquired Into			
			Direct and Collateral	Direct		Not Specified
				Parents and Grandparents	Parents	
Cooke and Vander Veer	Nonallergic	63	—	—	9.5%	—
Cooke and Vander Veer	Nonallergic	76	—	—	—	14.5%
Spain and Cooke	Nonallergic	115	—	—	—	7.0%
Balyeat	Nonallergic	403	—	—	9.0%	—
Cooke and Vander Veer	Nonallergic	504	48.4%	—	—	—
Spain and Cooke	Nonallergic	462	58.0%	—	—	—
Wiener, Zieve and Fries	Nonallergic	66	—	—	28.7%	—
Present Series	Allergic	250	54.4%	43.2%	22.4%	—

of eosinophilia made us feel that the negative results were due rather to the limitations of our methods than to an error in diagnosis. We have included seventy-three patients who were not completely tested; they were observed for a sufficient length of time to make us certain of the diagnosis, and the family histories are complete.

INCIDENCE OF POSITIVE FAMILY HISTORIES

It is generally stated that there is a 50 per cent incidence of positive family histories in allergic individuals. Figures in the literature range from 38.6 per cent to 71 per cent. In our 250 patients, we obtained a positive family history of allergy in 54.4 per cent. In Table I are presented the data of different investigators[1,3,4,5,8,14,15,18,26,31,33,44,45,46,47,52,59] together with our own. The average for all the studies listed in the table is 51.9 per cent.

When both the direct and collateral antecedents were included, 54.4 per cent of our patients had a positive family history (Table II). When questioned only with respect to the direct antecedents, i.e., parents and

grandparents, the incidence was 43.2 per cent. Limiting our inquiry still further to the presence of allergy in the parents of the patients, the incidence was reduced to 22.4 per cent. We calculated from the protocols of Wiener, Zieve and Fries,[59] who present data only for the fathers and

TABLE III.
INDIVIDUAL INCIDENCE OF MAJOR ALLERGY IN VARIOUS GROUPS OF THE FAMILIES* OF 250 ALLERGIC CHILDREN

	Total Numbers	Allergic Members	Incidence of Allergy
Total population of the families	6,244	617**	9.8%
Grandparents	1,000	71	7.1%
Parents	500	59	11.8%
Siblings	340	30	8.8%

*Average number of members and allergic persons per family were 24.9 and 2.5 respectively.
**Number includes the patient.

mothers of their allergic patients, that 28.8 per cent gave a positive history. From this tabulation, it becomes apparent that the figures vary in direct relation to the extent of the inquiry into the pedigree.

Both Rowe[45] and Vaughan[55] report that they have observed that the frequency of allergy in the family histories of individuals apparently devoid of allergic symptoms approaches that observed in allergic patients.

The wide discrepancy heretofore assumed to exist between the allergic and nonallergic groups, with respect to family history, may, therefore, be due to a lack of uniformity in definition and basis for statistical analysis rather than to a real difference (Table II).

INDIVIDUAL INCIDENCE OF ALLERGY IN SO-CALLED ALLERGIC POPULATION COMPARED TO RANDOM POPULATION

The allergic population in this instance is composed of the combined fraternities of our 250 patients. The families present a total of 6,244 individuals, including the patients (Table III). Of this total, 617 were allergic; the frequency of allergy in this "allergic" population, therefore, is 9.8 per cent. Bray[5] made a study of the families of 200 asthmatic children. There were 4,152 relatives, 14.3 per cent of whom were affected (Table IV). He included migraine as well as the four major allergic syndromes as allergic manifestations in the antecedents. This may account for the higher incidence.

An ideal random population to compare with the carefully studied allergic population should be a so-called normal group as intensively tested and questioned as the allergic group. In view of this insurmountable task, which normal patients would not subject themselves to, we (B. R.) carefully questioned 3,000 individuals. They comprised medical students, doctors and nurses over the years during the course of lectures. We limited

TABLE IV. INDIVIDUAL INCIDENCE (FREQUENCY) OF ALLERGY

Author	Nature of Inquiry	Total Population	Percentage
Bray	Allergy in relatives of 200 allergic patients, including asthma, hay fever, eczema, urticaria, angioneurotic edema, nettle rash, and migraine	4,152	14.3%
Ratner	Random questioning of medical students and nurses	3,000	10.0%
Present Study	Allergy (all major syndromes*) in parents only of 250 allergic patients	500	11.8%
Present Study	Allergy (all major syndromes) in the total population of 250 allergic patients and their relatives, direct and collateral (average of 24.9 members per family)	6,244	9.8%
Present Study	Asthma and hay fever in parents and siblings of 250 allergic patients	832	5.5%
Spain and Cooke	Asthma and hay fever in parents and siblings of 119 normal individuals (medical students)	387	3.6%
Cooke and Vander Veer	Allergy (all major syndromes) in 68 individuals, selected at random, and their parents	204	7.0%
Cooke and Vander Veer	Allergy (all major syndromes) in parents only of 68 unselected persons	136	6.6%
Cooke and Vander Veer	Allergy (all major syndromes) in parents only of 63 normal persons	126	4.7%
Balyeat	Asthma and hay fever in parents only of 403 normal University students	806	9.0%

*The major syndromes are asthma, hay fever, eczema, urticaria (and angioneurotic edema).

our questions to the presence of the four major allergic syndromes. It is interesting to report that invariably when groups of at least 100 were questioned, 10 per cent were allergic.**

The data on individual incidence of random groups vary markedly according to the criteria employed (Table IV). It appears quite generally agreed that about 7 to 10 per cent of the general population suffer from allergy[18,52] if the manifestations are limited to asthma, hay fever, eczema and urticaria (Table IV). We obtained figures ranging from 5.5 to 11.8 per cent in the so-called allergic population on our own cases, depending on the nature and scope of the inquiry.

When we considered only the parents of our patients, i.e., 500 individuals, we obtained 11.8 per cent. When our inquiry included the 250 allergic patients and their relatives, both direct and collateral antecedents, which totaled 6,244 persons, we obtained 9.8 per cent. When asthma and hay fever were the sole allergic disorders dealt with among the parents and siblings of the patients, 5.5 per cent was obtained. Spain and Cooke[52] found an incidence of 3.6 per cent when inquiry was limited to parents and siblings questioned for asthma and hay fever alone. When other allergic syndromes were included in the scope of their questionnaire, Cooke and Vander Veer found 7 per cent.

It is revealing that in the 500 parents of our allergic children only 11.8 per cent were allergic (Table III). In the 1,000 grandparents, 7.1 per cent were allergic. Furthermore, of the 340 siblings of the 250 allergic children, 8.8 per cent were allergic. It is of great significance that in the grand-

**Up to 13 per cent in the last few years.

parents, parents, and siblings of allergic children no greater incidence of allergy is found than that estimated for the random population.

This is of particular significance because all previous work has led us to believe that the individual incidence in so-called allergic families must be considerably higher.

Reference to Vaughan's paper[56] on minor allergies discloses that among 508 individuals in a small community who were personally interviewed by a trained social investigator, about 10 per cent suffered from major allergic manifestations, and approximately another 50 per cent gave a history of minor episodic allergic disorders. It is this latter group which again points up the question of criteria. (If it is valid to include these individuals in statistical studies, including those on genetics, then all published studies on incidence and heredity are seriously in error.)

From the foregoing, it is obvious that unless criteria are comparable, the evaluation of data with respect to the individual incidence of allergy is misleading, and the comparison of its magnitude in the families of allergic patients, the normal family, the allergic population, and random population is meaningless. At least when criteria are comparable, there appears to be no appreciable difference in the frequency of allergy in the so-called allergic population as compared with the random population.

Therefore, it may be stated that the incidence of major allergy in the random population is approximately 10 per cent. The frequency with which these syndromes occur in so-called allergic families or general populations is the same. About 60 per cent of the random population suffers from all forms of allergy, when one includes individuals with a history of minor episodic allergic manifestations.

INCIDENCE OF ALLERGY IN SO-CALLED ALLERGIC FAMILIES

The notion that one of the characteristic features of allergy is the great frequency with which it may appear in a family has been accepted and reiterated by many authors. A search for evidence in support of this idea reveals that it is based chiefly upon a few striking family pedigrees which have been recorded in the literature.[7,19,50]

Drinkwater[19] reported an incidence of 43 per cent in a family of twenty-three persons, ten of whom suffered from spasmodic asthma. The family described by Smith[50] had ninety-four members in five generations. There was an incidence of allergy of 56.2 per cent; the symptoms included hay fever, asthma, vasomotor rhinitis, urticaria, angioneurotic edema, and eczema. Her data was collected by the use of questionnaire. The pedigrees of a family of 454 members in five generations is presented by Bucher and Keeler,[7] of whom 102 (23 per cent) suffered from some form of allergy, including asthma, eczema, hives, hay fever, migraine, gastrointestinal upsets, allergic rhinitis and anaphylaxis. Attention is drawn to

TABLE V. NUMBER OF ALLERGIC MEMBERS PER FAMILY AS DISTRIBUTED IN 250 SO-CALLED ALLERGIC FAMILIES

Allergics Per Family:		1	2	3	4	5	6	7	8	9	10
Families	Number	99	63	33	16	18	14	5	1	0	1
	Per Cent	39.6%	24.8%	13.2%	6.8%	7.2%	5.6%	2%	0.4%	0%	0.4%

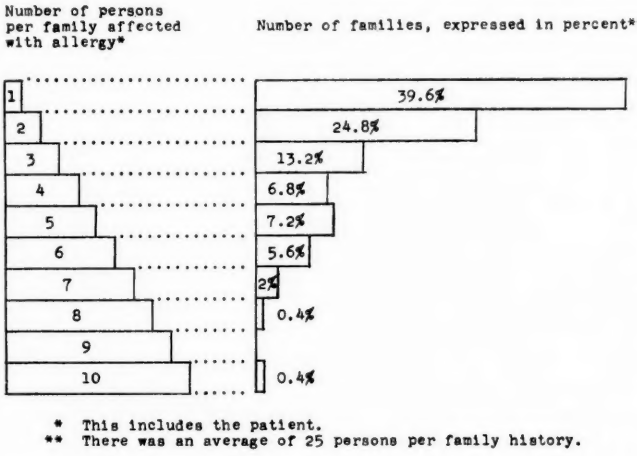

Fig. 1. The number of allergic members per family in 250 families of allergic patients, graphically shown.

the different criteria with respect to the interpretation of the allergic state in these three studies.

We present our own data in Figure 1 and Table V. Of the 250 families studied, ninety-nine (39.6 per cent) had one allergic member, who was the patient himself; 63 (24.8 per cent) of the families had two allergic members including the patient; 33 (13.2 per cent) of the families had three members. Hence the families which have only one to three allergic members, including the patient, comprise the large majority (77.6 per cent) of the entire group of 250 fraternities. When the data are analyzed, on the basis of the actual size of each family or the per cent of allergic members per family (Table VI), 88 per cent have an allergic membership of from 2 to 20 per cent, which is the incidence found in the general population (10 to 15 per cent); 11.2 per cent of the families have a positive incidence of from 20 to 40 per cent. The pedigree described by Bucher and Keeler falls into the latter group. However, only 0.8 per cent of the families have an allergic membership similar to the oft-quoted pedigree of Drinkwater, and that of Smith. This indicates the rarity of such an occurrence. It is not unreasonable to assume that if we by chance ques-

TABLE VI. PER CENT OF ALLERGIC MEMBERS PER FAMILY AS DISTRIBUTED IN 250 SO-CALLED ALLERGIC FAMILIES

Per Cent of Allergics Per Family:		2-10%	10-20%	20-30%	30-40%	40-50%	50-60%	60-70%
Families	Number	156	64	18	10	1	0	1
	Per Cent	62.4%	25.6%	7.2%	4.0%	0.4%	0%	0.4%
	Totals Grouped	88%		11.2%		0.8%*		

*Only two families, or 0.8% of the total number of families studied, showed an incidence of allergics per family comparable to the families of Drinkwater (43%) and Smith (56.2%).

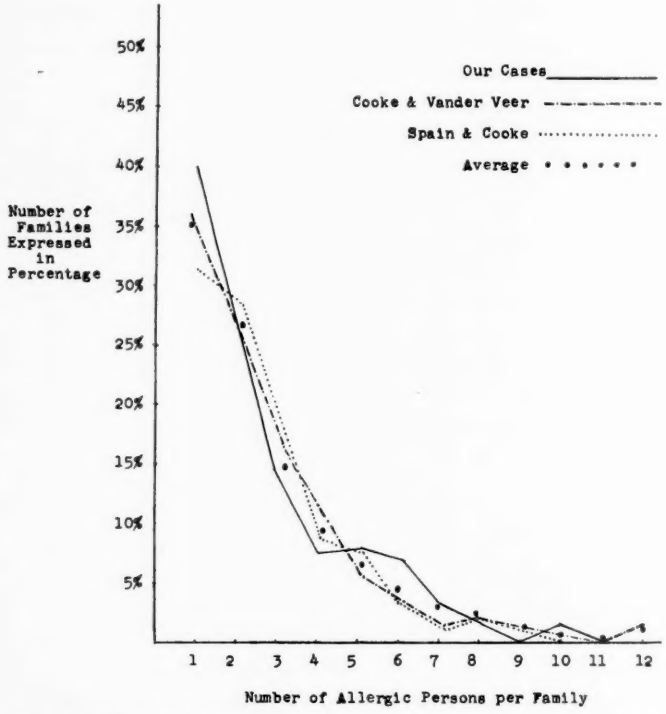

Fig. 2. Comparison of the number of allergic individuals per family in our cases, the cases of Cooke and Vander Veer, and of Spain and Cooke.

tioned one of the normal individuals in such a family, we would also obtain such a highly allergic family history.

We consulted the protocols of Cooke and his co-workers for their data on this point. Curves were plotted, and these were compared with the curve based upon our data (Fig. 2). It will be noted that the distribution of allergic members per family in their material is practically identical with ours.

TABLE VII. TYPE OF ALLERGIC FAMILY HISTORY IN RELATION TO NUMBER OF OFFSPRING AFFECTED BY ALLERGY

Type of Allergic Family History	Number of Families	Total Offspring	Allergic Offspring		Nonallergic Offspring	
			No.	%	No.	%
Bilateral	27	65	36	55.4	29	44.6
Unilateral on maternal side	63	140	77	55.0	63	45.0
Unilateral on paternal side	45	97	53	54.6	44	45.4
Negative	115	288	130	45.1	158	54.9
Totals	250	590				

We conclude, therefore, that while allergy may show a tendency to appear in fairly large numbers in certain few families, this cannot be regarded as representative of the general trend.

TYPE OF ALLERGIC FAMILY HISTORY IN RELATION TO NUMBER OF OFFSPRING AFFECTED WITH ALLERGY

When the incidence of allergic offspring in the family group is correlated with the type of family classified according to the presence of allergy in the branches (Table VII), we discover that a somewhat larger number of individuals are affected when it is present on both sides or one side than when there is a negative family history. A great deal of importance has been attributed to such distribution, and investigators have even gone to the point of predicting the numbers of offspring which must become affected according to Mendelian ratios. Most investigators continue to repeat these theoretical speculations.

In none of our calculations did we find that the actual number of allergic offspring corresponded with the theoretical expectations.

The figures of affected offspring are shown in Table VII. It is of interest to note that in families where allergy is present on both sides there is no higher incidence than when allergy is present on one side.

The bilateral group represents only twenty-seven families, or 11 per cent of the total number. A paucity of bilaterally affected families has been found by all investigators in this field. Therefore, families in which allergy will recur with sufficient frequency to make one suspect a genetic influence must necessarily be uncommon.

The oft-repeated statement that the age of onset of allergy is influenced by the frequency with which allergy occurs in the family (i.e., the greater the inheritance, the earlier will the age of onset occur) is not borne out by our previous study on this same material[35] and by those of others.[6,30,31]

SEX INCIDENCE IN ALLERGIC INDIVIDUALS

Figures for the sex incidence of allergy in both children and adults have been presented by many investigators. The data in the literature is not

entirely in agreement, and here too we find that variability in criteria have influenced the results.

Salter[46] attributed the preponderance of males over females, which he found, to environmental occupational factors. Bray[6] found that asthma is twice as common in boys as in girls, and that eczema is also more frequently found in boys, while hay fever is found with the same frequency. Among adults he found equal numbers affected with allergy. Bray believes that puberty must exert some beneficial effect upon the symptoms in the male and some deleterious effect in the female. Nelson,[29] using the age of onset, finds that before puberty there is a preponderance of males in the three groups, asthma, hay fever, and the dermatoses.

An analysis of the total child population in our series showed that the difference in the percentage of males having allergy as compared with female children was statistically significant. A similar study of the adults in the 250 pedigrees failed to show this difference. Our statistical findings, therefore, are in agreement with those of Bray.

We feel that the factors responsible for the sex differences found in children are too complex for us to analyze further.

COMMENT

A question will undoubtedly arise as to the validity of data derived from the study of children. An opinion has been voiced that the data obtained from studies in children may be subject to great error because, if the patient is an infant or a young child, the parents will be young and may not have arrived at the age at which allergic symptoms in the affected parent were destined to make their appearance.[12] If this criticism is valid and since allergy may develop even at the age of seventy, it would seem to us that no family history could be judged until each and every member had completed the entire span of his life. It should be recalled that at least 60 per cent of the allergies of adults start in childhood. Furthermore, were the contention just voiced correct, we would not have obtained 11.8 per cent in the parents and only 7.1 per cent in the grandparents. This would suggest that the older and more remote histories are less reliable.

It is our belief that more accurate family histories can be obtained for a child patient. The histories of the parents are certainly more accurate, especially if the parents can be interrogated personally, and there is a greater possibility of obtaining direct information from grandparents and collaterals. Wiener, Zieve and Fries[59] corroborate this. We might mention the fact that certain authors have asserted that they found positive family histories more frequently in children than in adults.[8,44]

Because of the complexities that exist, we believe that the questionnaire is not an acceptable method of eliciting information with respect to the family history in the problem of allergy. We feel that it is extremely important, in a study such as this, that the investigator must not only be

familiar with the conditions under scrutiny, but must also possess sufficient clinical knowledge to differentiate between conditions that are allergic and those that are not. Hanhart[20] also points out the inadequacy of the use of questionnaires in a condition such as allergy in which the complications are so numerous. The difficulties of this type of study are so great that even a worker of Pearson's importance may err, as pointed out by Wells.[58]

II. Hereditary Concept

The application of statistical technique in the study of human inheritance is beset with pitfalls. On the one hand, the experimental difficulties of the subject matter necessitate recourse to mathematical refinements which can be dispensed with in animal breeding. On the other, there is the danger of concealing assumptions which have no factual basis behind the impressive façade of flawless algebra.[22]

The tendency of asthma and hay fever to occur in families has been referred to repeatedly. In 1909, Drinkwater[19] described a family in which ten out of twenty-three individuals in three generations were afflicted with asthma. On the basis of this pedigree, he concluded that asthma is inherited as a simple Mendelian dominant character. A more extensive study was made by Cooke and Vander Veer[18] in 1916 to ascertain whether allergy occurs more frequently in some families than in others, and follows Mendelian laws. Adkinson subsequently published the results of an investigation which agreed with Cooke and Vander Veer in that genetic influences played a major role. Their point of difference was the interpretation of the mode of genetic inheritance. The former investigators came to the conclusion that hypersensitiveness is transmitted as a simple Mendelian dominant character, while the latter inferred that bronchial asthma is inherited as a simple recessive trait. Genetic transmission as a simple dominant character failed to explain why, in more than one half of the cases, no history of allergy could be elicited in any of the antecedents, either direct or collateral. The conclusion that bronchial asthma is inherited as a simple recessive trait was untenable, because of the presence of pedigrees in which both parents were affected, yet some children were normal.

In 1924 Spain and Cooke[52] presented additional material which, they felt, confirmed their original theory of the controlling influence of heredity, but this time suggested the possibility that the atopic factor is dominant and multiple, the component parts of which are separately inherited. Others[43] concluded that allergy is inherited as a simple dominant. Another contribution has been that of Wiener, Zieve and Fries[59] who postulate that there are two types of allergic individuals, supported by their bimodal distribution when classified according to the age of onset of symptoms. These authors suggest that there is the pure normal, the allergic individual whose symptoms begin before puberty, and the individuals who are either normal transmitters or who develop allergic disease after puberty.

While the foregoing represents a unanimity of opinion that genetic inheritance plays a major role in the pathogenesis of allergy, the genetic mechanism of the inherited factor could not be determined.

It is generally agreed that sensitization to specific proteins is not transmitted from the ascendant to the descendant, nor are the specific clinical symptoms. Further, the host factors thus far studied fail to show any physiological, immunological or chemical differences between allergic and normal persons.[25]

No one can refute the existence of a familial occurrence of allergic disorders. This is an experience observed by all clinicians. But it is of the utmost importance to obtain a clear understanding of the basis of this established clinical fact for both theoretical and practical reasons. It has been the practice of both biologists and clinicians to explain the phenomenon of the high familial incidence of any given trait on the basis of heredity.† Yet the definition of the term *heredity* in the past fifty years has come to denote certain extremely limited mechanisms. This has arisen as a result of the work of investigators who have devoted themselves to an achievement of better understanding of the reasons that offspring do show traits which resemble those of the parents, and the mechanisms which may explain the means by which these resemblances are transmitted.

These workers in the science of genetics are most notably represented by Morgan[27] and his school.[28] They elucidated the detailed mechanism of the transmission of characters by studies on the fruit fly. It is important to realize that in these studies the environmental conditions were rigidly controlled. Under these conditions and on the basis of cytological evidence and a large accumulation of statistical material, it was concluded that in the fruit fly, at least, many traits were transmitted from generation to generation according to the laws of Mendel, and that the determiners, or biochemical units, resided in the chromosomes or germinal material of the cell. Further, it was inferred from these studies that these determiners or genes had definite positions in specific chromosomes and that one could map the location of each determiner at a definite position on the chromosome. It should also be emphasized that the traits chosen for study were easily discernible anatomic landmarks which could be recorded in terms of number, shape, color, et cetera.

In spite of attempts at rigid control of the external environment, however, there appeared at times a trait totally different from that seen in preceding generations. The apparently spontaneous appearance of new

†In 1888, Spencer[53] stated that the inheritance of such diseases as gout, consumption, and insanity is universally admitted. Fifty-seven years later, Pinner[32] writes that tuberculosis both as infection and as disease is never inherited. Modern medical researches in tuberculosis, which include the isolation of the tubercle bacillus, the development of the tuberculin skin test, x-ray diagnosis, and a study of environmental factors, explain the total reorientation with regard to the role of heredity in the pathogenesis of tuberculosis.

traits was explained as a basic change in that portion of the chromosome which was presumed to be the actual determiner or representative of the fully formed character under scrutiny. The geneticists soon learned that these sudden changes (sports or mutations) could also be induced experimentally by varying experimental conditions, such as temperature and the application of chemicals or x-ray radiation at appropriate stages in the development of the organism.

The inference that may be drawn from this is that those mutations, which occurred in the ordinary course of an experiment under carefully controlled conditions, were also due to environmental changes, although more subtle, and at the present time beyond the control of the investigator. Environmental influences at any stage following the fertilization of the ovum play a very considerable role in determining what bodily traits shall be formed.

Prior to the clarification of the role of chromosomes and genes as carriers of traits from parent to offspring, the term *heredity* actually expressed the idea of like producing like. This concept implied that generally individuals of a species, or even of a variety, resembled each other so closely in the over-all that the likeness was unmistakable. No one could argue with this broad meaning of the term *heredity*, i.e., that the same general structure is reproduced.

We must reach agreement at the outset, however, on what we shall accept as the present definition of heredity. If we employ the broad concept that heredity expresses the idea that like produces like, then it would be reasonable to group the potentiality of man to become sensitized, or allergic, in the same class with other similarities which men possess in common, such as the biped habitus, the possession of seven cervical vertebrae, the ability to form antibodies, the ability to think in the abstract, and the characteristic of a nine-month period of gestation. Certainly not all of the foregoing traits are peculiar to man, but neither is the ability to become sensitized or allergic. The erect posture is peculiar to man, and in a broad sense this is his heredity, but we are not aware of any investigations which have attempted to show the Mendelian nature of this character.

The mechanisms concerned with the phenomenon of allergy in man have shown so far that sensitization falls within the broad domain of the antigen-antibody reaction. The ability of living things to respond to antigenic stimulation with the production of antibodies is widespread throughout the animal kingdom. It is one of the fundamental responses of living tissue, and is of the same order as growth, reproduction, and tissue synthesis. The allergic response is another facet of those mechanisms which ordinarily serve to protect and preserve the organism.

It is also imperative to arrive at a definition of the term *allergic*. Are the criteria solely clinical, or are positive laboratory data alone sufficient to establish the presence of the allergic state? Shall we include conditions

in which an immunologic mechanism cannot be demonstrated by all of the methods now available? Shall we include migraine, a single episode of transient urticaria, serum disease, and reactions to drugs?

It has been estimated that about 10 per cent of the population is allergic. This estimate, however, is based upon limited inquiry as to the occurrence of bronchial asthma, hay fever, eczema, urticaria, and clear-cut instances of allergic gastrointestinal disorders. It must be perfectly obvious that any valid appraisal of the role which genetic heredity plays in allergy must be predicated upon a correct definition of the allergy state in man. If this phase of the problem can be clarified, one must then demonstrate that this condition segregates and recombines in successive generations in the very definite, simple arithmetic ratios which Mendel first described.

A study of twins, particularly identical twins, has frequently been employed by investigators to evaluate the role played by heredity in a variety of clinical disorders and traits. Such a study was attempted by Spaich and Ostertag[51] regarding allergy, and their conclusion was that heredity is a dominant factor.

Careful perusal of this work is not convincing. The authors used the hazardous method of the questionnaire. Although they eliminate one third of the cases collected because of inaccuracies, we are inclined to exclude many more. An example of such is the following:

"Females 47 years old. One twin had hay fever from the age of 20. At the age of 24 years, she was treated for stomach ulcer and at 29 had rheumatic joints. The sister, at 25 and 31 years of age, was treated for gallstones, which are found very frequently in allergic families, but she never had hay fever. One sister of the twins had bronchial asthma; the mother had gallstones; one brother of the mother had stomach ulcers. The maternal grandfather had asthma. Two children of the twin with hay fever also had hay fever."

The authors conclude that these identical twins have no concordance of allergic disease but have a concordance of allergic disposition. Can one accept gallstones as an indication of allergic disposition? These authors seem to regard as equivalents of the usually accepted allergic syndromes such ill-defined conditions as stomach trouble, weak stomach, rheumatism, migraine, gall-bladder disease, undetermined skin eruptions, psychotic conditions, gout, diabetes mellitus, and inebriety.

They found in hay fever that with identical twins there was an 80 per cent concordance of disease and 100 per cent concordance of allergic disposition. With the nonidentical twins there was no concordance of disease but 100 per cent concordance of allergic disposition. These percentages were obtained on the basis of five pairs of identical twins and two pairs of nonidentical twins, numbers which we believe do not warrant statistical treatment.

With asthma, the results showed greater variability. In 28.6 per cent of

the identical twins, there was asthma in both, and in only 57.1 per cent was an allergic disposition found in both. With the nonidentical twins, only 7.1 per cent had asthma in common, while 57.1 per cent had an allergic disposition in common.

Discussing the investigations of identical twins in relation to the problem of inheritance of cancer, Little[24] quotes two studies which purport to indicate that the incidence of similar tumors in both members of a pair of identical twins is greater by far than would be expected by chance distribution alone.

"It must, however, be pointed out," he states, "that such data prove little if anything concerning the genetics of such tumors. There are few, if any, facts showing that twins developed a type of tumor which had appeared in one or both parents or grandparents. Without such comparative data on successive generations, the evidence provided by similar histories of twins is limited in application. All that can be said is that origin of monovular twins from the cells descended from a single fertilized ovum which develop with a single placental contact with the maternal parent may produce similar ontogenic histories. Theoretically, if cancer were due to an agent or agents present in a fertilized ovum or in maternal blood in a form transferable through the placenta, the same result would be expected. Such an agent might be a gene, a part of or a whole chromosome, or any component of a reproducible type in the egg cytoplasm, or a viroid or serological substance of maternal origin. Similarly, if cancer required as one of its etiological factors any agent or substance transmitted through the milk or by direct contact with the mother, twins of any sort would be exposed under essentially the same physiological and mechanical conditions in the mother. The common origin of the monovular twins might then be a discernible factor in producing a similar response to such stimuli."

We have already mentioned the universal response throughout the animal kingdom to the invasion of the organism by antigen by the conserving and protective production of antibodies. In 1925, Coca and Grove[13] set apart the Prausnitz-Küstner antibody, whose presence was first demonstrated by its reaction in the human skin with its corresponding antigen. They called this antibody *atopic reagin* on the thesis that it was unique in that it was found only in the natural or inherited type of allergy. It is not our purpose here to develop the relative merits of the unitarian hypothesis of antibodies and the atopic theory, except to point out that the later hypothesis rests on a most vulnerable base, namely, the inheritance of the allergic diseases. It is, however, pertinent again to present here certain data which were previously reviewed by one of us.[34]

It is unquestioned that serum sickness is solely an acquired disease resulting from the injection of a foreign serum protein. The so-called atopic reagin (P-K antibody), which was thought to be related only to the so-called natural atopic sensitization, has undeniably been found in this artificially acquired allergic syndrome, and by some of the proponents of the hereditary hypothesis. Thus, Cooke and Spain[17] successfully demonstrated the atopic reagin to horse serum to be present in the blood of serum

sickness cases. At about the same time, Tuft and Ramsdell[54] reported a larger series of cases. They found a close correlation with other allergic antibodies found in the sera in serum disease. Lippard[23] also found P-K antibodies in serum disease.

Cooke and Spain clearly state the problem by asserting that there is no warrant for assuming any difference in the biological reaction of natural and artificial sensitization in the sense that the reaction is mediated by an antibody mechanism in both. As far as Tuft and Ramsdell could determine, the behavior of the antibody concerned in these P-K reactions was in every way identical with that of the atopic reagin studied by Coca and Grove.

Other proponents of the atopic theory, confronted with these striking observations,[21] stated that there is no acceptable evidence that any of the known antibodies which have been found in the blood in the course of serum disease are responsible for that condition. The presence of these antibodies, however, cannot be regarded as meaningless. As we view it, their presence epitomizes the antigen-antibody mechanism, and the fact that these antibodies are found in a solely acquired condition, such as serum sickness, can mean but one thing: that immunologically, at least, no proof is at hand that a purely acquired allergic phenomenon such as serum sickness can be differentiated from the so-called inherited form of allergy (atopy).

Present-day knowledge of human inheritance is meager and unsatisfactory. Direct experimental methods available in botany and zoology are obviously impossible in man. In plants and in lower forms of insect life experimental matings can be made to determine the operation of the laws of heredity, the mode of transmission of various characters, and their modifiability in the presence of other characters. In the study of human inheritance we are not confronted with pure lines, but with the most complicated admixture of different lines. Matings are random; the genetic constitutions of the parents entering into the matings are not known. The breeding period is so delayed that it is seldom that any one observer can watch the effects of the condition on more than two generations. The number of offspring are so few that there are seldom enough children to express all of the possibilities of the mating with respect to any one character.

The student of human inheritance, therefore, is limited to a study of pedigrees to observe the incidence of pathological disorders. Much of the evidence on which these deductions rest is based on hearsay. Records are generally inadequate, not always accurate, and certainly liable to subjective interpretation by the investigator. Bullock and Fildes,[9] in their study on hemophilia, called the most heritable of human diseases, relate two instances in which divergent results were reported by two different observers on one and the same family, made within a few years of each other.

In view of the conflicting conclusions that have been drawn by different

investigators thus far in an attempt to apply Mendelian laws to allergy, the difficulty in obtaining adequate material, and the inadequate definition of essential criteria, we agree with Hogben[22] that no hypothesis can be made to fit the existing data. Chase,[11] commenting on the subject, states that, indeed, with certain allergies such as hay fever, the genotype of the individual has been said to exert absolute control over the capacity for sensitization; this matter has not yet been subjected to adequate experimentation.

III. Pathogenesis of Allergy

On the positive side, evidence is at hand which shows that unaltered allergens may enter the blood via many portals. Antigens and antibodies may be transmitted to the fetus transplacentally.[37,38,39,40,42] Unaltered proteins may pass through the walls of the digestive tract[41,48,57] or the respiratory tract.[2,10,36,49] Unaltered allergens may enter the blood stream by way of the skin or by parenteral injection.

It should be made clear that allergy stems from invasion into the body of foreign substances and is an acquired condition in the same sense that an infectious disease is. It is impossible, therefore, to exclude insidious previous invasion of allergens in any given case of allergy.

All individuals are potentially capable of developing allergy. Many factors, varying from time to time in the same individual, make for a greater or lesser vulnerability to its development. We must consider that the inception of allergy depends to a large extent on quantitative exposure and, further, that the exposure must occur under favorable circumstances: i.e., when the tissues are more permeable for physiologic reasons or as a result of preceding pathology. The antenatal period, infancy, and periods of disease and convalescence constitute vulnerable times when the individual must be protected from undue exposure to highly antigenic substances.

Man battles continually against the invasion of foreign proteins and haptenic substances. The difference between the normal individual who battles successfully and the allergic who does not, may be more quantitative than qualitative, if we grant that *quantitative* applies to the amount of antigen which actually penetrates the tissue cells and not the amount to which the individual is exposed.

If human allergy is acquired, therefore, we must look into the many facets of the modes of acquisition and the insidious ways in which sensitization can arise, and not view allergy as stemming from and dominated by genetic influences.

As is pointed out by Zinsser and Bayne-Jones[60]:

> "It is almost forced upon one to conclude that what is inherited is the capacity for being sensitized, and this is a phenomenon quite common in the animal kingdom, where the energy of antibody production is rarely the same in two animals injected with identical amounts of the same antigen."

The acquisition of hypersensitiveness, we believe, depends upon: (1) changing factors which make for a greater receptivity of the tissue for allergens, (2) the nature of the exciting substance, (3) the amount of allergen to which the individual is exposed, (4) the amount of allergen which actually invades the blood stream, and (5) the intervals at which exposures occur.

SUMMARY AND CONCLUSIONS

1. The discrepancies noted in published observations on the distribution of allergy and its relation to heredity and the inferences drawn therefrom are largely due to the different methods of collection of data, the criteria employed in defining the allergic state, and the extent to which inquiry was made into the individual and family incidence of allergy.

2. A positive family history was obtained in approximately 50 per cent of our allergic patients and of those reported in the literature.

3. About 10 per cent of persons in the random population, in the so-called allergic population and in the parents, grandparents, and siblings of the allergic children studied, have major allergies.

4. About 50 per cent of the random population have minor allergies.

5. The concept that it is characteristic of allergy to appear in a large number of members of so-called allergic families is not supported by our data. While allergy may appear in fairly large numbers in certain few families, this is not the general trend.

6. The age of onset of allergic symptoms is not influenced by the freqency with which allergy occurs in the antecedents.

7. In the child population there was a significant greater number of males with allergy. The adult population failed to show this difference.

8. In view of the conflicting conclusions that have been drawn by different investigators thus far in an attempt to apply Mendelian laws to allergy, the difficulty in obtaining adequate material and the inadequate definition of essential criteria, no genetic hypothesis can be made to fit the existing data.

9. Inferences drawn from studies on twins with regard to genetic influences are not necessarily valid.

10. The atopic theory, which postulates a special antibody under hereditary influence, is untenable.

11. All individuals are potentially capable of developing allergy. Whether an individual develops allergy or not depends more upon quantitative than qualitative considerations, if we grant that *quantitative* applies not to the degree of exposure but to the amount of antigen which actually penetrates the tissue cells.

12. The acquisition of hypersensitiveness depends upon (a) changing factors which make for a greater receptivity of the tissues for allergens, (b) the nature of the exciting substance, (c) the amount of allergen to

which the individual is exposed, (d) the amount of allergen which actually invades the blood stream, and (e) the intervals at which the exposures occur.

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DERMATITIS MEDICAMENTOSA SIMULATING HODGKIN'S DISEASE DUE TO MERCURY COMPOUNDS

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EXPLOSIVE constitutional symptoms as well as cutaneous manifestations may result from drug allergies. It is not unusual for heavy metals to produce toxic symptoms sufficiently grave to be dangerous or even on occasion to cause death of the patient. These constitutional symptoms may take many forms, but a generalized reaction from mercury simulating Hodgkin's disease has not been previously reported, as far as could be ascertained.

Numerous cases of mercury poisoning have been previously reported in the literature. In these, however, sufficient amounts of mercury had been absorbed to produce generalized toxic reactions; but reports of severe, acute, generalized reactions due to an allergic response to a relatively innocuous type of mercury compound applied to the intact skin are quite rare. A careful survey of the literature revealed very few cases of this type. The severity of the reaction in this particular case and the fact that it was for some years considered to be Hodgkin's disease make its recording desirable.

REPORT OF CASE

The patient when first seen was acutely ill. His temperature was 104.6° F. He presented a generalized scarlatiniform erythema which was edematous and associated with considerable suborbital edema. He complained of photophobia, sore throat, headache, and joint pains. The conjunctivae and pharynx were injected. Cervical, axillary, epitrochlear, and inguinal lymph nodes were palpable, rubbery, freely movable, and not tender. A dry, hacking cough was present which caused him much discomfort.

Laboratory data including roentgen ray examinations revealed normal findings with the exception of peripheral blood studies. The erythrocyte count was 5.4 million, hemoglobin 110 per cent, leukocyte count 10,300, with 6 per cent eosinophilia. Blood cultures were negative after twenty-four hours and seven days.

Within three days after admission to the hospital all signs and symptoms began to fade, and within ten days the patient was completely well. He volunteered the information that he had Hodgkin's disease, the diagnosis having been made in 1934 and confirmed during another acute episode in 1937. He did not, however, understand the gravity of such a diagnosis. Cervical glands had been removed for biopsy on both of the above dates, and since the patient was reluctant to undergo additional biopsies, a report and slides of these two biopsies were requested for further study. For the sake of brevity and clarity the summary of his second admission is reproduced.

The slides from these biopsies did not resemble those of true Hodgkin's disease. The architecture seemed fairly well preserved except in local areas. This local destruction seemed to be the result of a hyperplasia of the monocytes. No Dorothy Reed giant cells were demonstrable. The slides, however, were old and the stain had faded considerably. No fresh sections were available.

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Out of fairness to the original pathologist, however, it should be emphasized that not infrequently chronic lymphadenitis accompanying an exfoliative dermatitis may simulate an atypical Hodgkin's disease. The reverse is also true: namely, what at first seems to be a simple inflammatory lymphadenitis subsequently may reveal typical Hodgkin's disease.

The pathological picture was considered to be some form of acute leukosis and, according to the pathologist, an atypical form of Hodgkin's disease. A careful history revealed some very illuminating aspects. At the time of his first attack, he had used "blue ointment" for pubic pediculosis. Three years later, another episode was preceded by treatment of some vesicles on his chin with a white ointment prescribed by a druggist. Between the above attack and the time of this last episode, he had had two additional attacks. Before one of these, his brother, who shared his room, had been using "blue ointment" for pubic pediculosis.

Somewhat similar circumstances preceded his present attack. Although the patient was unaware of it there were several men in his barracks who were using "blue ointment" for pubic lice. He had been in the barracks less than two days when he suddenly became acutely ill. This started with malaise, sore throat, cough and fever. After approximately twenty-four hours, however, he developed the cutaneous erythema, which began at the back of the neck with a feeling of heat and then spread to the rest of the body.

Investigative Data.—In order to determine whether this strange association of mercury with these episodes had any significance, it was decided to test him with mercurials. After all signs and symptoms had abated, a small pea-sized amount of 5 per cent ammoniated mercury ointment made up in petrolatum was rubbed into the skin of the anterior abdominal wall. Within four hours after this inunction, the patient's temperature started to rise. At this time the ointment was washed off with acetone followed by soap and water. The temperature continued to rise, however, and reached 104.6° F. in an additional four hours. A diffuse erythema started at the back of the neck and then spread over the body. Coryza-like symptoms appeared. In twenty-four hours the lymph nodes became palpable, and in forty-eight hours the liver was felt two finger-breadths below the right costal margin. The temperature began to drop and symptoms subsided after two days. Within seven days all signs of the reaction had disappeared.

After a lapse of several more days a small pea-sized amount of 1 per cent calomel ointment was rubbed on the anterior abdominal wall. What followed was a repetition of the above. In both instances following the inunction of mercurial compounds a local contact dermatitis was not produced at the site of inunction.

The reason for these acute attacks was explained to the patient and to his family, who were now aware of the gravity and prognosis of Hodgkin's disease. He was soon discharged to full duty and at the end of the war was still on active duty as an infantryman and apparently in good health.

The sequence of events in the above case invoked a curiosity of the possibility of other cases of dermatitis medicamentosa which may have been considered Hodgkin's disease, and the nature of their final disposition.

Keith[2] in 1937 described a very similar case in a gardener who handled heavy metals as sprays. Tests were made with arsenic but not with mercury. The patient died, and a diagnosis of Hodgkin's disease was made post mortem. The section of the lymph gland in this case more closely resembled Hodgkin's disease than did the section from the above case; the architecture of the gland was almost completely destroyed. There was

considerable eosinophilia, and monocytes were liberally mixed with the lymphocytes. Against the diagnosis of Hodgkin's disease, however, was the absence of Dorothy Reed giant cells, and the presence of extreme vascularity.

In 1940,[1] at the meeting of the Minnesota Dermatologic Society, a case of universal exfoliative dermatitis with hyperpigmentation and adenopathy was presented. During the previous four years, the patient had had occasional attacks of regional dermatitis which lasted several weeks. During these attacks, abnormal amounts of arsenic were found in the urine. Examination revealed a leukocyte count of 10,000 to 16,000 with 6 per cent monocytes and 13 per cent lymphocytes. O'Leary classified this case as a low grade form of lymphoblastoma. Generalized exfoliative dermatitis from arsenic is not unusual, but it is frequently impossible to differentiate it from a lymphoblastomatous process. An accurate diagnosis in such cases requires frequent observation and correlation of clinical, histological (i.e., biopsy skin and lymph nodes) and hematological findings.

In 1944 Samitz[3] reported a case with reaction to 10 per cent ammoniated mercury which paralleled this case except that there was no enlargement of the liver.

One of the editors of the *Year Book of Dermatology*[4] saw a case of psoriasis in which 3 per cent ammoniated mercury applied only once to hands and elbows led to a long-lasting and almost fatal erythroderma with cardiac, renal, and other visceral complications.

SUMMARY AND CONCLUSIONS

1. A case of universal scarlatiniform erythema with hyperpyrexia and generalized lymphadenitis from absorption of mercury following local topical application is reported.

2. The unusual features in this case are the extreme sensitivity to mercury, the reproduction of the symptoms by local inunction of mercurials, and the mistaken diagnosis of Hodgkin's disease.

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THE INCIDENCE OF ALLERGY IN PERSONS WHO HAVE MANY COLDS

A Controlled Study

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WITH the advent of the antihistamines and their use in the treatment of the common cold,[1] considerable interest was revived in the role of allergy in respiratory infections. Prior to the antihistaminic era, occasional investigators from time to time postulated that allergy in some way or other influenced or caused frequent respiratory infections.[2,4,5,8,12] Aside from their studies, it is easy to understand how a lay person or even a physician might easily misdiagnose an allergic manifestation such as pollinosis or perennial allergic rhinitis for the common cold. Furthermore, it seems probable that the edematous allergic respiratory mucous membranes with resulting secondary obstruction would provide a fertile ground for secondary bacterial and perhaps viral infections. On the basis of these studies and the above reasoning, the authors undertook the present study to determine the proportion of allergic individuals in a selected group who were considered to have frequent respiratory infections as compared to a control group who had infrequent respiratory infections.

METHODS

The first group, those considered to have frequent respiratory infections, which will henceforth be designated the susceptible group, were selected from Eastman Kodak employes solely on the basis of their history of having had frequent "colds." With the realization that the term "colds" entails numerous clinical conditions as interpreted by various individuals, and since the data was obtained from histories rather than from direct observations, the authors used the word "colds" in its widest sense to include the entire spectrum of minor upper respiratory infections. Individuals who had a history of having five or more "colds" per year were included in the susceptible group. After the participants had been selected, a detailed allergic history was taken on a special form to keep the questions as uniform as possible. Nasal smears for eosinophils were taken from all subjects.

The second group, those considered to have infrequent respiratory infections, which will henceforth be designated as the control group, were selected from Eastman Kodak employes who had two or less colds per year. Histories and nasal smears for eosinophils were done in the same manner as with the susceptible group.

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The nasal smears were stained by the Hansel method[11] and read by one of the authors. In order to standardize this part of the investigation as much as possible, a thorough examination of the slide was made, and the number of polymorphonuclear cells and the number of eosinophil cells in four representative areas of the slide under oil immersion were counted and recorded. An over-all percentage of eosinophils was then estimated. In practice the authors did not calculate the percentage, but merely recorded the number of polymorphonuclear cells over the number of eosinophils. This method of recording has been found to be simpler and easier to interpret than Hansel's method of "plus marks." If 10 per cent or more of the cells were eosinophils, the smear was considered to be positive.

In evaluating the individual's history and the family history with regard to hypersensitivities, only the following major allergic conditions were considered: asthma, pollinosis, perennial allergic rhinitis, and eczema. Urticaria and angioneurotic edema were not included because in the authors' experience they occur frequently in persons who show no other allergic manifestations and very often cannot be proven to be of allergic origin. Other allergic conditions, as gastrointestinal allergy, migraine, physical allergies, and rheumatic states, were not used in evaluating the results because they are less easily recognized and in many instances these manifestations cannot be proven to be manifestations of atopy.

RESULTS

A total of 186 employes, eighty-nine females and ninety-seven males, were included in the susceptible group: those individuals who had five or more colds a year. Their ages ranged from eighteen to sixty-five years, the average age being 33.7 years.

The control group consisted of 118 employes, sixty-six females and fifty-two males, all of whom had two or less colds a year. Over 80 per cent of this group actually claimed they had one or less colds a year. Their ages ranged from twenty to sixty years of age with an average of 34.4 years.

TABLE I

	No.	Pos. Family History	%	Pos. Personal History	%	Pos. Nasal Smears	%
Susceptible Group	186	40	21.5%	36	19.3%	15	8.0%
Control Group	118	22	18.6%	12	10.1%	7	5.9%

In Table I the results of the allergic histories and nasal smears are summarized. Forty of the susceptible group (21.5 per cent) gave histories of parents or siblings with asthma, hay fever, perennial allergic rhinitis, or eczema. Twenty-two (18.6 per cent) of the control group had a positive family history. Although the susceptible group did have a higher per cent of positive family histories for the above-named conditions, the difference between the two, 2.9 per cent, is insignificant.

Thirty-six (19.3 per cent) of the susceptible group had a history of having had one or more of these major allergic conditions as compared to twelve (10.1 per cent) of the control group, with a difference of 9.2 per cent. The per cent of allergic individuals in the control group agrees with most other authors' estimates or studies that about 10 per cent of the population have major allergic conditions. It is also in accordance with the percentage of ragweed pollinosis in high school children of Rochester, New York, as determined by a recent survey by some of the present authors.[10]

Nasal smears for eosinophils were taken from all members of both groups. Surprisingly little difference, 2.1 per cent, was found between the two groups.

However, when all three factors—the family history, the individual's history, and nasal smears—were considered together as evidence of atopy, a probable significant difference between the two groups is noted. Thirty-eight and one-tenth per cent of the susceptible group had one or more positive findings for one of the above factors as compared to 25.4 per cent of the control group. In other words, the susceptible group had 12.7 per cent more individuals than the control group who had either a history of allergy in their family, or a major allergic condition themselves, or a positive nasal smear.

COMMENTS

In evaluating the results of this study, the authors recognize certain inherent dangers in taking data primarily from clinical histories and not from actual observations over a period of time. For example, Diehl, Baker, and Cowan[7] reported a reduction of 63 per cent in the number of colds the patients had had the year before their study to the period of the study. In following the susceptible group for over a year's time as part of another study, the authors also found that the subject on the average had about 50 per cent fewer colds than he claimed to have had in the past.

Another very limiting factor to our study was the relatively small number of subjects surveyed in both the study and the control groups.

A correlation of physical findings with the other data would have added greatly to the validity of the results. This is not reported because not all subjects of both groups were examined completely or by the same physician, and hence a completely objective comparison of physical findings could not be made. The authors also felt that the nasal smears for eosinophils, which have been shown to correlate highly with the appearance of the mucous membranes, would be a reflection of the appearance of the mucous membranes in an objective way.

In Table I the difference between the percentage of positive nasal smears in the two groups is very slight, 2.1 per cent, and the percentages did not correlate well with the positive personal histories of allergies. There may be several reasons for this: First, not all smears may have been properly made, and, therefore, some may have been falsely negative. Secondly, not

all smears were taken at the same time, thus leading to further discrepancies. For example, a pollinosis patient might not give a positive smear except during the pollinating season, and an asthmatic patient might give a positive smear only when he had come in contact with the specific allergens causing his difficulty. Actually, the percentage of positive smears in the susceptible group was higher than shown in Table I because repeat smears of some of the originally negative subjects were positive. These individuals were not included in the figures because repeat smears were not made from all subjects, and the comparison between the two groups would have been less valid. Lastly, the history of an allergic condition was not confirmed in all cases by actual observations and findings.

As was pointed out above, the syndrome of the "common cold" was used in its widest sense to include any kind of upper respiratory infections. Admittedly, this is not very scientific, but the purpose of this paper was to find out if there were more allergic individuals in a group complaining of having many "colds." As judged by the family history, a history of allergy in the individual, and nasal smears for eosinophils, there was approximately 10 per cent more allergy in this group. It is conceivable that this increase in percentage could be attributed solely to an error in diagnosis by the subject, that is, diagnosing his allergies as a "cold." Whatever the reason may be, however, it seems advisable that one should consider allergy in the differential diagnosis of a person complaining of frequent "colds."

To the authors' knowledge, there have been very few investigations of allergy and its relationships to colds; and the results of this study are not comparable to those of Coca's[5] and to Brown's et al,[3] as they studied the incidence of the common cold in relation to nonreaginic food allergy which consisted of urticaria, headaches, heartburn, indigestion, canker sores, dizziness, diarrhea, nervousness, neuralgia, and physical tiredness. Most of these symptoms would not be considered by us as allergic manifestations; and urticaria, for reasons previously stated, was excluded.

Fox and Livingston[9] found in their studies that over 80 per cent of subjects susceptible to the common cold were allergic or of an allergic family. They did not define such terms as *susceptibility* and did not present the details of their study. In their classification of allergy, they included clinical and subclinical allergies or borderline allergies. The latter was diagnosed by the findings of hyperplastic nasal mucous membrane changes in a person with a history of allergy or in whose family there is a history of allergy and in whom a foreign protein survey reveals positive reactions to particular allergens. By using their criteria for allergy, many more of the authors' study and control groups would have been considered allergic. A control group added to the investigations of Fox and Livingston would have been helpful in interpreting and evaluating their results.

In 1931 Cohen and Rudolph[6] presented an excellent table of fundamental importance differentiating infectious and allergic conditions of the upper respiratory tract (Table II). The points made are by no means constant

TABLE II

(Cohen and Rudolph[6])

History	
Allergic	*Contagious*
1. Attacks usually recurrent.	1. Attacks usually single.
2. Often mild symptoms between attacks.	2. Usually clears up completely.
3. Definite relation to heredity.	3. No relation to heredity.
4. Not contagious.	4. Contagious.
5. Not related to exposure to another case.	5. Definite relation to exposure to another case.
6. Constitutional symptoms slight.	6. Constitutional symptoms more marked.
7. Foods and inhaled substances often traced as causes.	7. No relation to foods or inhaled substances as cause.
8. Itching common.	8. No itching.
9. Wheezing common.	9. No wheezing.
10. Other allergic conditions present or in past history.	10. Usually no other allergic condition present or in past history.
Examination	
Allergic	*Contagious*
1. Visible mucous membranes pale, glistening, edematous.	1. Visible mucous membranes, hyperemic, red.
2. Thin, watery, mucoid nasal discharge, mucoid sputum.	2. Mucopurulent or purulent nasal discharge and sputum.
3. Smear shows eosinophils 10% or more.	3. Smear shows polymorphonuclear neutrophils as predominant cell; eosinophils few or absent.
4. Other signs of allergy often present.	4. No other signs of allergy.
5. Sinus involvement of hyperplastic type.	5. Sinus involvement of purulent type.
6. Wheezing breath sounds.	6. No wheezing breath sounds.
7. Roentgenogram shows bronchial markings increased.	7. Bronchial markings not increased on roentgenogram.
8. Allergic skin reactions usually positive.	8. Allergic skin reactions usually negative.

for all cases, and one must evaluate all the factors—history, physical findings, and therapeutic response—before making a diagnosis. From this present study and from our experience we would like to add these additional comments. Although major allergic conditions unquestionably occur on a hereditary basis, they occur so frequently among the general population that a positive family history alone does not necessarily indicate an allergy. About 20 per cent of both susceptible and control groups in this study had positive family histories for allergies. To the symptoms of itching and wheezing, sneezing and coughing should also be added.

SUMMARY AND CONCLUSIONS

Allergic histories and nasal smears for eosinophils were taken from 186 Eastman Kodak employes who gave histories of having frequent "colds" (five or more) and were compared to those of a control group of 118 employes who had two or less "colds" a year.

No significant differences were found in the percentage of positive family histories for allergies or of positive nasal smears. Of the group susceptible to "colds," 9.2 per cent more had a history of asthma, allergic rhinitis, pollinosis, or atopic dermatitis as compared to the group with infrequent "colds." When all three factors—family history, personal allergic history, and nasal smears for eosinophils—were considered together as indices of atopy, a difference of 12.7 per cent was found.

The limitations of this study have been discussed and the results compared to other investigators' reports. In view of these limitations the re-

sults of this study should not be viewed as a final answer; nevertheless, they do suggest that the complaint of frequent "colds" is found more often in individuals with definite allergic conditions, and a causal relationship between the allergic constitution and the incidence of "colds" is therefore suggested.

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MISSISSIPPI VALLEY MEDICAL SOCIETY 1952 ESSAY CONTEST

The Twelfth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1952. The Society will offer a cash prize of $200.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Contestants must be members of the American Medical Association and residents and citizens of the United States. The winner will be invited to present his contribution before the Seventeenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Missouri, October 1, 2, 3, 1952, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal*. All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5,000 words, annd must be received not later than May 1, 1952. The winning essays in the 1950 contest appear in the January, 1951, issue of the *Mississippi Valley Medical Journal* (Quincy, Ill.).

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W.C.U. Bldg., Quincy, Illinois.

URTICARIA DUE TO POLLEN

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IN a survey on the causes of urticaria[8] a number of cases were encountered in which pollen was found to be the precipitating agent. Indeed, from this survey it appeared that more persons might have had hives from pollen than from food.

About twenty years ago, one of us noted that on certain days when the pollen count was high, a larger number of urticaria patients than usual were seen at the office. Either their condition had been very acute, or it had been chronic with a distinct aggravation on such days.

The literature has, on the whole, disregarded pollen as cause of urticaria. Sulzberger,[5] admitting that determining the etiologic approach in chronic urticaria is rarely successful, did not mention pollen as a possible cause. In one of the most comprehensive and thorough analyses on urticaria by Hopkins and Kesten[4] no mention was made of pollen. Urticaria from inhalants, they believed, was surprisingly rare and uncertain. In a recent article by Graham and Wolf[3] on the psychosomatic aspect of hives, the possibility of inhalants, especially of pollen, is entirely disregarded. In a survey on 159 cases, Evans et al,[2] recently noted that inhalant factors were responsible in only 7.3 per cent as compared with 14.4 per cent in which food was suspected.

The first case of urticaria from pollen was reported by Taub and White[6] in 1931. Their patient had no evidence of hay fever. The hives failed to appear when the patient avoided golf courses and tennis courts.

The strongest support of our point is made by Tuft,[7] who notes that hay fever patients develop seasonal urticaria limited solely to the pollinating season. He believes that inhalant allergens, including pollens, are more frequently the cause of hives than is generally appreciated.

It has been proven experimentally that urticaria can be elicited by inhalation of pollen. Cohen et al[1] induced flare-ups of passive transfer sites on the skin, in other words, hives of temporary duration, by blowing ragweed pollen into the nose of individuals whose skin had been sensitized. No experimental data are available on the production of urticaria of longer duration by a prolonged influx of pollen into the blood stream through the portals of nasal and bronchial mucous membranes as it occurs during the hay fever season.

The following are typical case reports.

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Case 1.—R. L. G., a fifty-five-year-old dentist, was seen in September, 1943, with hives which had been present since August 13. They were associated with nasal catarrh and occasional pain in the chest. He had had hay fever in early life which had cleared up spontaneously. Among other possible sources he had a chronic prostatitis, an acute tonsillitis one week prior to the onset, and a diseased tooth. Elimination of foods suspected as a cause, extraction of the suspected tooth, treatment for the prostatitis had no effect on the hives. The condition improved gradually and cleared up completely by October 9.

During 1944 and 1945, the hives recurred about August 15 and subsided promptly with the first frost. Another attack of urticaria occurred in June, 1946, when the patient had been using a garden spray which contained pyrethrum. On repeated intradermal skin tests, a number of reactions were obtained, among which pyrethrum and both ragweeds (30 units) reacted 2-plus. Treatment for ragweed was started in July. It was possible to reach a dose of 6,000 units after eight doses of ragweed extract. After this preseasonal treatment in 1946, complete subsidence of the hives ensued, with exception of a minor flare-up in September, 1949.

Comment.—The seasonal occurrence of the urticaria, the prompt response to pollen treatment, and the history of previous hay fever which had disappeared spontaneously, point to ragweed as the primary cause. The fact that urticaria also occurred following inhalation of pyrethrum suggests that multiple sensitivity was at play.

Case 2.—E. B., a fifty-six-year-old woman was seen in July, 1947, after having moved to Detroit from Chicago. Her hives developed about June 1. Two previous episodes in midsummer of 1945 and 1946 had lasted about two to three weeks. There had been a history of a perennial nasal catarrh. There was also a ringworm infection on her toes which was suspected as the cause. An allergic survey by another allergist revealed positive reactions to foods and such fungi as Alternaria, rust, Monilia, and Curvularia. Dietary restrictions and such nonspecific treatment as intramuscular typhoid vaccine and histamine injections were said to have been of no avail.

While she was under my care, her symptoms cleared up without treatment. The following summer (1948) she returned with very severe hives involving the whole body surface. Symptomatic treatment, especially epinephrine and ephedrine, gave temporary relief. She was retested for pollen, fungi, and food and showed 4-plus reactions to a mixture of 30 units of timothy, orchard grass and June grass. After three daily injections of 30, 50, and 80 units, her symptoms began to disappear and did not recur during the season.

In February, 1949, the patient returned for a course of preseasonal treatment. A mixture of dry grass pollen was blown into her nose. Within ten minutes a severe generalized outbreak of hives occurred, associated with marked rhinorrhea. This lasted for about forty-eight hours. On May 23, when the first grass pollen appeared in the air, she again developed marked urticaria. She was then treated with small doses (½ unit) of grass pollen, three to four times daily for three days. This controlled her symptoms completely.

Comment.—This patient had an allergic nasal disease before the occurrence of seasonal hives. The etiology was proven by the production of urticaria through insufflation of powdered grass pollen. The subsidence of the symptoms following a few small doses of pollen extract coseasonally is of interest.

Case 3.—Miss R. M. P., forty-four years of age, was first seen in October, 1945, with urticaria which occurred mostly at night and affected buttocks, legs, and both arms. The history failed to reveal any source of this condition. The patient had had ragweed hay fever for about fifteen years. For the past eight years this had been completely controlled by pollen injections. However, during the past three years urticaria occurred in place of hay fever. It usually started about August 15; it was particularly severe when the patient was taking a bath.

Because the history suggested that ragweed was the major cause of hives, the patient was given three injections of 10 units of ragweed daily for two days. During the course of these injections, the hives disappeared completely. On November 3, ragweed pollen was blown into the patient's nose by means of an atomizer. Within fifteen minutes, severe urticaria occurred on arms, legs and trunk, which subsided following administration of 0.1 cc epinephrine.

During the following years the patient was treated with ragweed injections preseasonally, a final dose of 20,000 units being reached. After the 1948 ragweed season perennial treatment was initiated with intervals of four to six weeks between injections. In 1949, on August 13, she again developed urticaria. The last dose of 20,000 units had been given three weeks previously. Repetition of this dose promptly cleared up the hives. Another acute attack occurred about September 15. Further pollen injections, injections of histamine, and an elimination diet based on new skin tests, were of no avail. This condition persisted throughout the early part of the winter 1949-1950, when it cleared up spontaneously. In 1950 another recurrence took place following an injection of ragweed extract (20,000 units) given at the height of the ragweed season (September 5). This condition did not clear up before January, 1951. During the entire time of observation, this patient had been completely free from hay fever.

Comment.—In contrast to Cases 1 and 2, this patient's hives persisted after the ragweed season and did not respond to treatment with pollen extract. That they were originally brought on by ragweed is suggested by their clinical course, by the experimental production of the hives through insufflation of pollen, and by their recurrence following an injection of ragweed extract which probably constituted an overdose at this particular time of the season. During the past two years, the patient developed various secondary sensitizations. Upon skin testing, she reacted to many antigens. It is our impression that the larger doses of pollen extract aggravated the patient's state of sensitization and her tendency to hives.

The clinical course in these three cases paralleled closely that of twenty-three additional ones recorded in Tables I and II. In the twelve cases presented in Table I, the hives were confined to the pollen season; in the fourteen of Table II, they originated during the pollen season and persisted throughout the following months. In two individuals, they subsided coincidentally with the first snowfall. Such secondary factors as foods, fungous infections, insect bites, ingestion of salicylates, and aggravation of the hives by the menstrual period were noted to be instrumental in the protraction of hives. This conforms with our observation on other chronic allergic diseases. In chronic asthma, for instance, symptoms are often inaugurated by pollen and persist for many months after.

The ages of the patients ranged between eleven and sixty-six. In thir-

TABLE I. URTICARIA CONFINED TO POLLEN SEASON

Case No.	Name Sex Age	Allergic Background		No. of Seasons	Seasonal Incidence	Intrad. Skin Reaction to Suspected Pollen	Treatment with Pollen Extract	Remarks
		In Family	In Patient					
1	Mr. R.L.G. 55	—	H.F.	5	Aug. through Oct.	Ragweed ++	Effective	
2	Mrs. E.B. 56	Son—H.F.	H.F.	5	June	Grasses ++++	Effective	*
3	Mrs. S.C. 34	—	H.F. Contact Dermatitis	3	April	Oak Walnut ++	Effective	
4	Mrs. S.B. 19	Brother—H.F.	Allergic Nasal Dis.	2	Aug./Sept.	Ragweed ++	Effective	*
5	Mrs. R.W. 28	—	Migraine	2	Aug. 15 to Sept. 10	Ragweed ++	—	* Spontaneous clearance
6	Mrs. H.K. 27	—	Allergic Nasal Dis.	3	June/July	Grasses ++	Effective	
7	Mrs. C.S. 39	—	—	2	May/June Aug. through Oct.	Grasses +++ Ragweed ++	No Relief	*
8	Miss E.K. 11	Father—Asthma	—	2	June	Grasses ++	—	
9	Mr. E.B. 41	Sons—Asthma Urticaria Eczema	H.F.	2	July to frost	Ragweed +++	—	*
10	Miss B.B. 21	Father—Asthma	H.F.	9	Aug. to Sept.	Ragweed +++	Effective	
11	Mrs. R.S. 41	—	H.F.	2	June/July	Grasses +++	No Relief	* Hives when mowing lawn
12	Mrs. McG. 18	Brother—H.F.	H.F.	5	Aug. 15 through Oct.	Ragweed ++	Effective	Started after overdose of pollen extract

H.F.—Hay fever.
*Insufflation of dry pollen into nasopharnyx.

teen an allergic family history was recorded; fifteen of the twenty-six patients had hay fever or perennial allergic nasal disease; two had other allergic manifestations.

The hives had been present for an average of 3.3 seasons. In twelve the symptoms occurred during the ragweed season; in thirteen during the pollination of the grasses; one patient had urticaria from tree pollen. On intradermal testing, the majority reacted very strongly to the pollen which were in season at the time of the symptoms. All patients gave additional skin reactions to antigens other than pollen.

All but three patients in Table II, and all patients in Table I, were treated with pollen extract. The effect of the treatment is recorded only in Table I since in the other cases its evaluation was too difficult to permit satisfactory conclusions. As a rule, the hives cleared up after two to three injections. Some patients remained symptom-free throughout the season, whereas the hives recurred in others after one to two days and required additional injections. In the two patients of Table I, in whom no improvement ensued, we feel that the pollen extract was administered in too large doses. One

TABLE II. URTICARIA LASTING PAST THE POLLEN SEASON

Case No.	Name Sex Age	Allergic Background		No. of Seasons	Onset of Hives	Reactions on Intradermal Skin Testing	Remarks
		In Family	In Patient				
1	Miss R.M.P. 44	—	H.F.	5	Aug. 15	Ragweed + +	*
2	Mrs. A.R. 39	—	Allergic Nasal Dis.	2	May and Aug.	Timothy + + Ragweed + + +	* Symptom-free in California
3	Mrs. W.R. 51	Son—Urticaria	—	4	June	Grasses + +	Hives following blood transfusion
4	Mr. G.V. 25	Brother—Eczema	—	3	Aug. 15	Ragweed + + Pigweed + +	*
5	Mr. P.B. 13	Father—H.F.	Allergic Nasal Dis. Contact Dermatitis	7	June/July	Grasses + + +	
6	Mrs. H.P. 34	Sister—Migraine	Gastro-intest. Allergy	3	May	Yellow + + + Dock	*
7	Mr. B.G. 31	Father—Asthma	Allergic Nasal Dis.	3	Aug. 15	Ragweed + +	
8	Miss M.A. 18	Father—H.F.	—	2	Early June	Grasses + +	* Aggravated by cold temperature
9	Mrs. C.H. 39	—	—	3	Aug. 15	Ragweed + +	
10	Mrs. N.I. 52	Brother—Asthma	—	3	May Aug.	Grasses + + Ragweed + +	*
11	Mrs. M.T. 38	—	Allergic Nasal Dis.	2	June	Grasses +	*
12	Mr. T.V. 33	Son—Eczema	—	3	June	Grasses + +	
13	Miss P.P. 16	—	—	3	May/July	Grasses + +	
14	Mr. R.H. 37	—	Allergic Nasal Dis.	2	May	Grasses + +	*

H.F.—Hay fever
*Insufflation of dry pollen into nasopharynx

must guard carefully against giving a dose in excess of the patient's tolerance.

In the cases in which the evidence that pollen caused the urticaria appeared inconclusive to us, powdered pollen was blown into the patient's nose as indicated in the last column of both tables. It should be noted that urticaria was reproduced within ten to thirty minutes in every instance in which this was done.

DISCUSSION

It is very difficult to present adequate statistics on the incidence of pollen as the cause of urticaria, in view of the fact that patients may react to a single antigen or to a group of antigens. Table III represents an attempt at evaluating the causes of recurrent and chronic urticaria, in a series of ninety-four patients, published elsewhere.[8] These were the cases which showed definite clinical features of allergy, as contrasted with sixty-four in

which such evidence was absent. Twenty-two of the ninety-four were due to pollen as compared with eighteen caused by foods. According to this analysis, it appears that pollen as a cause of hives should be given much greater attention.

TABLE III. PRINCIPAL CAUSES OF CHRONIC HIVES IN PATIENTS EXHIBITING SATISFACTORY SKIN REACTIONS*

		Number of Cases
Pollen		22
Food		18
Inhalants other than pollen		13
Ingested and inhaled antigents combined		15
Injections:		
Liver extract	2	
Vitamin B	1	
Insulin	2	5
Endocrine:		
Premenstrual urticaria		3
Contact:		
Cat hair	2	
Hair setting lotion	2	
Nail polish	3	
Human dander	2	9
Drugs:		
Aspirin	8	
Ephedrine nasal spray	1	9
		94

*From survey on hives by Waldbott[8]

CONCLUSION

Twenty-six cases of urticaria are presented in which clinical evidence pointed to pollen as being the principal causative factor. In twelve the hives were confined to the pollen season; in fourteen they were protracted by what appeared to be secondary factors. Seasonal onset, periodic recurrence, positive skin reactions, and reproduction of hives by insufflation of powdered pollen into the nose characterized these cases.

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602 Professional Building

ALLERGIC CATARACT

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JUVENILE cataract associated with dermatitis was reported as long ago as 1868 by Rothmund.[8] Further observations have shown that juvenile cataract may be found in: (a) atopic dermatitis or neurodermatitis, (b) scleroderma, (c) the so-called Rothmund syndrome (poikiloderma atrophicans). The case here reported falls within the first group, juvenile cataract associated with atopic dermatitis.

CASE REPORT

A young woman, single, twenty-one years old, had a history of skin disturbances, first observed when she was four months old, localized to the flexor surfaces of elbows and knees, and behind the ears. Since then these disturbances appeared periodically, increasing in severity and frequency, with added infection at certain times. Approximately three years ago asthmatic symptoms appeared, which have increased in severity fairly rapidly. No significant hereditary or familial antecedents were reported. Physical examination showed no abnormalities, besides eosinophilia in the nasal smear and disturbances in the eyes reported below. Cutaneous tests and pK test gave positive results with the following antigens: (a) foods, marked: chicken meat, corn, strawberry; slight: potato, asparagus, cocoa, peanut, and barley; questionable: milk; (b) inhalants, marked: flaxseed; slight: cat and horse dander, house dust, and orris root; questionable: pollens and molds.

Approximately a year ago (June, 1950), the patient noticed failing eyesight, especially in the right eye, and consulted an ophthalmologist. No disturbance in the eyes had occurred before this. Physical examination of the eyes showed opacities in both lenses, more marked in the right eye. Microscopic examination showed that the opacities are situated in both lenses immediately deep to the anterior capsule of the lens, in front of the anterior disjunction band. They occupy a central situation with respect to the pupil and appear as a shield-like plate with irregular margins, of a bluish-white color (Fig. 1). The opacity in the right eye is larger than in the left. The capsule in the neighborhood of the opacity appears to be wrinkled. There is also slight radiated striation of crystalline fibers. The patient reports subjective improvement and deterioration in her eyesight coinciding with the condition of her skin, but objectively no significant changes were observed.

A diagnosis of atopic dermatitis or neurodermatitis associated with cataract which can be classified as an allergic cataract, was therefore established.

COMMENTARY

Juvenile cataract in cases of atopic dermatitis is an infrequent occurrence; Tuft[7] found a total of only sixty-one cases reported up to 1947. Brunsting[3] found atopic dermatitis in 10 per cent of the cases with juvenile cataract. In 30 per cent of the cases of allergic cataract the lesion is found in only one eye. There is no difference in frequency or severity between the sexes. Cataract always appears after dermatitis has been established, and in the second or third decade of life or later. According to Beetham[1] opacity of the lens may begin: (a) in the posterior pole of the lens advancing towards the anterior cortex, as in typical cataract; or (b) as a shield-like

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central opacity under the anterior capsule, commencing in the second or third decade of life. The case here reported belongs to this second type, which Vogt[10] considers is characteristic of juvenile allergic cataract associated with atopic dermatitis. There is no difficulty in establishing a differential diagnosis between juvenile allergic cata-

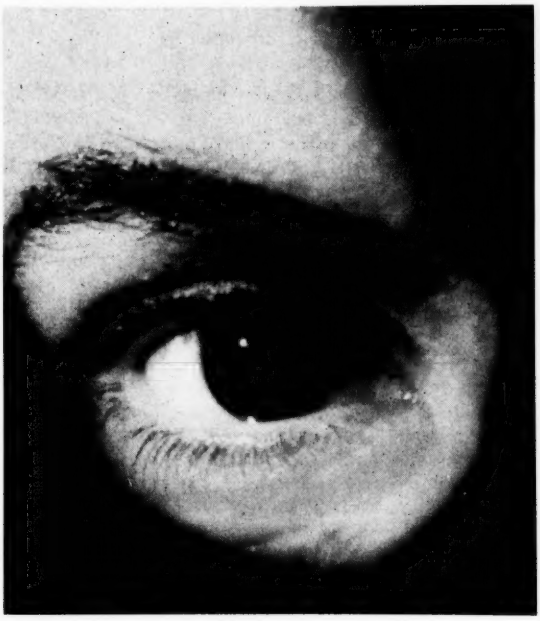

Fig. 1.

ract and congenital or traumatic cataract, as the case history differs and association with a previously existing dermatitis is constant in the former.

The allergic origin of certain juvenile cataracts is not universally admitted. Thus Bothman and Cooke[2] maintain that hereditary, endocrine, and nutritive conditions which may influence the development of opacity in the lens are not sufficiently known to be discarded as causative agents in cases classified as allergic cataract. Of course, in all cases before such a diagnosis is established, other causes should be discarded. Urbach and Gottlieb[8] consider that the existence of cases of allergic cataract cannot be disputed. The name of allergic cataract was not used until Daniel introduced it in 1935.[6]

There is no definite explanation of the mechanism which causes cataract in these cases. The most generally accepted hypothesis is that the patient suffers from atopy, i.e., allergic sensitiveness to certain allergens (Coca).[4] According to Vaughan[9] certain tissues or organs, varying with the patient, act as shock effectors responding with greater intensity to sensitization.

Cases of juvenile cataract associated with atopic dermatitis occur in atopic subjects, in whom the allergic reaction takes place in the skin and lenses, both arising from the ectoderm and acting as shock effectors. Reaction to the allergen is neuro-

(Continued on Page 39)

HEMIPLEGIA AND ALLERGIC SYMPTOMS FOLLOWING INGESTION OF CERTAIN FOODS

A Case Report

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THE patient was a woman, single, twenty-nine years old. Four years ago she began to suffer from attacks of expiratory dyspnea, which were nonseasonal. Approximately three years ago the patient suffered in addition from painful swellings of the joints, diffuse urticaria and erythema, paresis in the fingers, and a rise in temperature to 37.5° to 38° C. (100° to 100.4° F.). This process lasted for about one year, during which time there were no attacks of asthma. When these symptoms disappeared, bronchial stenosis was again evident. Both these syndromes alternated, swelling of the joints being accompanied by edema in the eyelids, cheeks, lips, and tongue. There were also signs of capillary fragility: petechiae and ecchymosis of the legs and thighs, constituting a purpuric syndrome.

There is a familial history of minor allergy, but no other significant hereditary or familial disturbances. Examination of nasal secretion revealed nothing abnormal, but the white blood count showed 16 per cent eosinophils. Skin tests were negative. Weight was 40 kilograms. Height was 1.59 meters. On January 10, 1946, immediately after a meal, which was by no means large, the patient became dizzy and fell. When examined, hemiparesis on the right side was observed; also paralysis of the right abducens nerve, lower right facial paresis, and dysarthria. Edema, urticaria, and purpura became more marked. The symptoms disappeared rapidly, but twenty-four hours later the attack was repeated with the same characteristics.

Physical examination in hospital showed paralysis of the abducens muscle of the right eye, lower facial paresis on the right side, paresis of the right arm and—less marked—of the right lower limb; dysarthria; tendon reflexes active. There was congenital strabismus of the right eye and nystagmus. Bleeding time and blood clotting time were normal. Laboratory tests were negative, except that the blood count showed 34 per cent eosinophils. The patient gradually improved and was dismissed from hospital on January 27. On March 22 a third attack identical with the previous two occurred. The only abnormality besides those recorded, found in a very thorough physical and laboratory examination, was an eosinophil count of 40 per cent and 15 mg p.c. albumin in the urine.

The patient was given a saline cathartic, large doses of ascorbic acid intravenously, and a diet free from wheat foods. The symptoms disappeared almost completely in a few days. In order to establish the existence of sensitivity to wheat, the patient was given food with wheat flour on March 29 and within a few hours began to suffer from headaches; later edema and purpuric signs appeared in both legs. Wheat products were eliminated, and the same treatment as on the previous occasion was given. Three days later the patient was normal. To confirm this result and discard fortuitous coincidence, the patient was again given wheat foods on April 6. Edema, purpura, and this time expiratory dyspnea were provoked, which disappeared when wheat foods were eliminated. On April 19 a third test with the ingestion of wheat gave the same results; in this case pruritus, edema, and marked purpura were the salient features. A fourth test gave the same result. Passive transfer was tried but failed to demonstrate reagins.

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COMMENTARY

Osler (1888)[3] described a case in which repeated attacks of hemiplegia and aphasia, associated with purpura, urticaria, and angioneurotic edema, were observed. A few similar cases have later been reported, the majority of which coincided with allergy to certain foods. Keeney's[1] case of hemiplegia following epinephrine injections is similar to these.

The nervous system in these cases is a shock effector in sensitized subjects, the cerebral disturbances being due to angioneurotic edema according to Foster Kennedy.[2]

SUMMARY

A patient suffered repeated attacks of hemiplegia associated with disturbances such as edema, urticaria, purpura, and bronchial stenosis, which were proved to be caused by the ingestion of certain foodstuffs. Nervous symptoms disappeared with allergic reactions when the causative foodstuffs were eliminated from the diet.

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(Doctor Bentolila)

ALLERGIC CATARACT

(Continued from Page 37)

dermatitis in the skin and opacity in the lens. An allergen may cause only a reaction in the lens, i.e., a cataract, or may be the cause of several allergic syndromes, provoking disturbances in the permeability of the capsule of the lens as a first stage in the formation of a cataract.

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FURTHER STUDIES ON THE EFFECT OF HISTAMINE ON THE MARCHIAFAVA-MICHELI SYNDROME

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THE term *idiopathic hemolytic anemia* has become a catch basin for many strange anemic pictures. In this group the paroxysmal nocturnal hemoglobinemia is placed by many. However, because of the numerous specific characteristics of the disease, it no doubt should be separated from the other idiopathic anemias. The syndrome has been very evasive as to definite etiology, although most workers believe as we do that the disease is an allergic phenomenon, even though the antibodies have never been proved to be present. This is the reason why we, in attempting to study that disease, have used histamine and now cortisone and ACTH.

CASE REPORT

Since our last report[7] the patient continued to have repeated bouts of hemolysis, the course of each one being reversed by the administration of histamine. The anemic picture ranged between 40 and 50 per cent hemoglobin, and red cell counts varied between 1.6 and 2.3 million cells.

In September of 1949 we attempted, without success, to obtain ACTH or cortisone for a therapeutic trial, for it was our belief that in this condition we were dealing with either a primary or a secondary adrenal insufficiency. Once these drugs became available we decided once again to weigh their effects on the paroxysmal nocturnal hemoglobinuria.

Believing the adrenals to be exhausted or in a state of exhaustion after the repeated stress of hemolysis, as described by Selye,[6] we administered cortisone. On January 31, 1951, our patient (Fig. 1) showed the typical paroxysms resulting in dark-colored urine and a red cell count of 2.3 million cells with a hemoglobin of 50 per cent. The Ham-Horack test[3] revealed negative hemolysis in tubes one and two but positive hemolysis in three and four. Initial administration of 100 mg of cortisone was initiated for five days, and on the fourth day heavy hemolysis occurred throughout the entire day. On the sixth day we again administered 2.75 mg of histamine in 250 cc of glucose intravenously. The following day we gave 500 cc of whole blood because the red cell counts had dropped to 1.6 million with a 30 per cent hemoglobin and the reticulocytes showed only 1.2 per cent response. We became especially alarmed because of the lack of reticulocyte response, which before the cortisone regime had ranged from 20 to 40 per cent. As we had usually found, the color of the urine the day following the giving of histamine returned to the paroxysmal character, and two days later the urine became clear (on February 7).

Since it became apparent that cortisone could not prevent the hemolysis, nor could it stop the process, we decided to initiate ACTH therapy on February 8. We gave 80 mg daily for four days (Fig. 2), while the urine remained clear. The blood counts at that time were 42 per cent hemoglobin and 1.8 million cells. On the fifth day we reduced the dose to 20 mg of ACTH daily and continued this daily dose until February 19. The urine remained clear the entire period; therefore, we discontinued the drug. Two days later the dark urine returned in paroxysms, but on the fourth

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Doctors Stefanic and Loyke are members of the staff of St. John's Hospital, Cleveland, Ohio.

Date	% Hb.	RBC	Medication	Color of Urine: Morn.	Aft.	Eve.	Night
2-7-51	42%	1.9 m	---	0	0	0	0
2-8-51	42%	1.8m	ACTH 80 mg.	0	0	0	0
			" (4 days)			0	
2-12-51				0	0	0	0
2-13-51	48%	2.4m	ACTH 20 mg.	0	0	0	0
			" (8 days)				
2-19-51				0	0	0	0
2-21-51			No medication	0	0	0	5
2-22-51				5	5	5	5
2-24-51	59%	3.1 m	ACTH 20 mg.	5	5	5	5
2-26-51				5	0	0	0
2-27-51	40%	2.1 m		0	0	0	0
			(17 days)				
3-3-51				5	0	0	0
3-4-51	52%	2.8 m		0	0	0	0
3-21-51	71%	3.2 m					
4-2-51			No medication	0	0	0	5
4-3-51			" " ACTH 20 mg.	5	0	0	0
4-6-51				0	0	0	0
4-10-51	68%	3.3m					
			(25 days)				
4-12-51				0	0	0	5
4-13-51				0	0	0	0
4-20-51	70%	3.4 m					
4-28-51	76%	3.8m		0	0	0	0

Key --- 1. clear 4. brown
2. pink 5. black
3. red

Fig. 1.

Date	% Reticulocytes	% Hb.	RBC.	Medication	Color urine			
					morn.	aft.	eve.	nite
1-22-51	37%	47%	2.2m		5	5	0	0
1-30-51		50%	2.3m		5	5	5	3
1-31-51				Cortisone 100mg	0	0	0	0
2-1-51				"	0	0	0	0
2-2-51				"	0	0	0	0
2-3-51	.05%	46%	2.3m	"	5	5	5	5
2-4-51				"	5	5	5	5
2-5-51	1.2%			Histamine	5	5	5	5
2-6-51		32%	1.8m	500 cc. Blood	5	5	3	0
2-7-51		42%	1.9m		0	0	0	0

Key--- 1- Clear
2- Pink
3- Red
4- Brown
5- Black

Fig. 2.

day the heavy spill was again noted. We again started the ACTH therapy in daily injections of 20 mg, and after four days the urine again became clear (February 27). Our counts at that time were 40 per cent hemoglobin and 2.1 million red cells. After four days of clear urine the morning sample of March 3 was dark, but then the urine remained clear for nineteen days. At the termination of the ACTH therapy on March 21 the patient's counts had risen to a level never attained during the two years of observation, namely, 71 per cent hemoglobin and 3.2 million red cells. The patient stated that for the first time since he had acquired the disease, he actually felt well, even in comparison with other previous periods free from paroxysms.

The urine remained clear for ten days following the completion of the ACTH therapy. On the eleventh day (April 2) the paroxysmal spill returned. Again we gave daily injections of 20 mg of ACTH, and three days later the urine became clear throughout the entire day. The urine remained clear for six days, and on the following day (April 12) a single nocturnal spill occurred. The counts at this time were 68 per cent hemoglobin with 3.4 million red cells. The urine has remained clear, and on April 20 the counts again rose to 70 per cent hemoglobin with 3.4 million red cells.

It was our belief that we were dealing in part with a primary or secondary adrenal insufficiency because of the continued stress of the hemolysis, and we attempted to prove the contention by following the Thorn test as described by Thorn[1] in 1948.

In June of 1950, since we could not obtain ACTH and because of Selye's[6] statement that epinephrine normally raises the corticotropin with resulting eosinopenia, we administered the test with 3 minims of parenteral adrenaline. The adrenaline was given after a total eosinophil count was performed, and this was followed by a second total eosinophil count in four hours. We noted that during the occurrence of heavy hemolysis over a period of days (Fig. 3) no peripheral eosinophils occurred initially, but in the four-hour sample of the test there would be a rise in the total eosinophils. With improvement, as shown by periods free of hemolysis, there were initially 55 to 77 total eosinophils respectively. As we had longer periods free of

Date.	Color urine.	TEC 1.		TEC 2.	% Hb.	RBC	Medication
5-30-50	Black 5 days	0		18			
5-31-50	Clear 1 d.	0	Adrenalin	133	24%	1.1m	
6-5-50	Clear 6d.	0		111	39%	1.7m	Adrenaline
6-10-50	Black 3d.	0		33			
6-16-50	Black 9d.	0	3 min.	11			
7-5-50	Clear 15d.	55		88	61%	3.0m	
7-17-50	Clear 25d.	77		100			
11-10-50	Clear 30 d. Black 1 d.	77		66	25%	2.5m	Histamine
1-13-51	Black 3d.	77	C.	55			Cortisone
2-9-51	Clear 4d.	111	ACTH	55	42%	1.9m	ACTH
2-14-51	Clear 15d. Black 3d.	210		66			ACTH
3-4-51	Clear 6d.	199	20mg	99	52%	2.9m	ACTH
4-10-51	Clear 5d.	122		33	68%	3.3m	ACTH
4-20-51	Clear 8d.	133	A	99	70%	3.4m	ACTH

Fig. 3.

Date	% Reticulocytes	Medication	% Hb.	R. B.C.
4-27-50	26%	Histamine	36%	1.7m.
5-9-50	44%		35%	1.8m.
5-20-50	25%		35%	1.7m.
11-20-50	35%	Histamine	35%	2.5m.
12-20-50	37%	Histamine	42%	1.7m.
2-3-51	.05%	Cortisone	46%	2.7m.
2-8-51	2.9%	ACTH	42%	1.7m.
2-13-51	.09%	ACTH	48%	2.4m.
3-4-51	1.7%	ACTH	52%	2.9m.
4-10-51	1.2%	ACTH	68%	3.3m.
4-20-51	1.0%	ACTH	70%	3.3m.

Fig. 4.

hemolysis we approached a normal response with a moderate fall in the second sample. Note must be made that we likewise had improvement in the disease at this time, for there was no dark-colored urine for approximately one month. Following the medication with both cortisone and ACTH, we administered the test with cortisone and ACTH separately. During this period we observed for the first time a normal

response to the Thorn test. To confirm the improvement in the response to the test and to verify the use of epinephrine, we injected the latter in the same period as that of the ACTH and obtained a positive Thorn test with this substance also.

We would like to call attention to the effect cortisone and ACTH had upon the reticulocyte counts, which were performed using a vital stain.[5] Preceding the administration of either cortisone or ACTH we had obtained reticulocyte counts ranging from 26 to 44 per cent (Fig. 4). Following the administration of the two drugs, the counts ranged from .05 per cent to 2.9 per cent with a mean average of 1.19 per cent.

DISCUSSION

In a previous article[7] we published a preliminary report on the use of histamine in a case of hemolytic anemia exhibiting the Marchiafava-Micheli syndrome. At that time it was noted that antihistamines were of no value, probably because, as Gordonoff[2] reported, they do not, at least immediately, reduce the amount of circulating histamine in the blood. Since histamine treatment had a strikingly modifying effect on the course of the disease, the following data will be of added interest.

Histamine has been used in the treatment of a variety of diseases grouped chiefly under the so-called allergic pattern, and Horton[4] has given an excellent review of its action and efficacy in a recent article. It is his belief from extensive use over a period of many years that its main effects are produced through vasodilatation throughout the body. Although this would not necessarily explain its value in this case of anemia, we are in accord with the concept that this substance exerts metabolic effects as yet only partially and inadequately explained. Mobilized free histamine in the blood presumably provokes (through vasodilatation or direct stimulation) an added release of epinephrine which then stimulates the pituitary through the hypothalmus to activate the adrenal cortex (Fig. 5). Therapeutically histamine has, however, a great advantage over epinephrine in that untoward effects can be controlled with adequate and prolonged usage and in that it introduces other beneficial results (vasodilatation, et cetera) which in themselves probably effect generalized organic response. In the limited number of normals we tested we have reason to believe that the eosinopenic response is the same as that obtained with adrenaline, ACTH and cortisone. Horton[4] also makes mention of this eosinopenic response. The use of ACTH in this patient produced as noted below a markedly beneficial change in the blood picture after cortisone failed to do so. Had this been the reverse, we might have postulated adrenal cortical fatigue. In place of that concept we may assume that the steroid spectrum of stimulation of the adrenal cortex contains a factor or factors not represented thus far by cortisone or other substitution therapy. When cortical fatigue was present at a later date, cortisone also produced beneficial results.

It is noted that the chemical structure of the factors which stimulate the adrenal cortex are quite variable, while the spectrum resulting from stimulation (which includes cortisone, et al) contains chemical substances

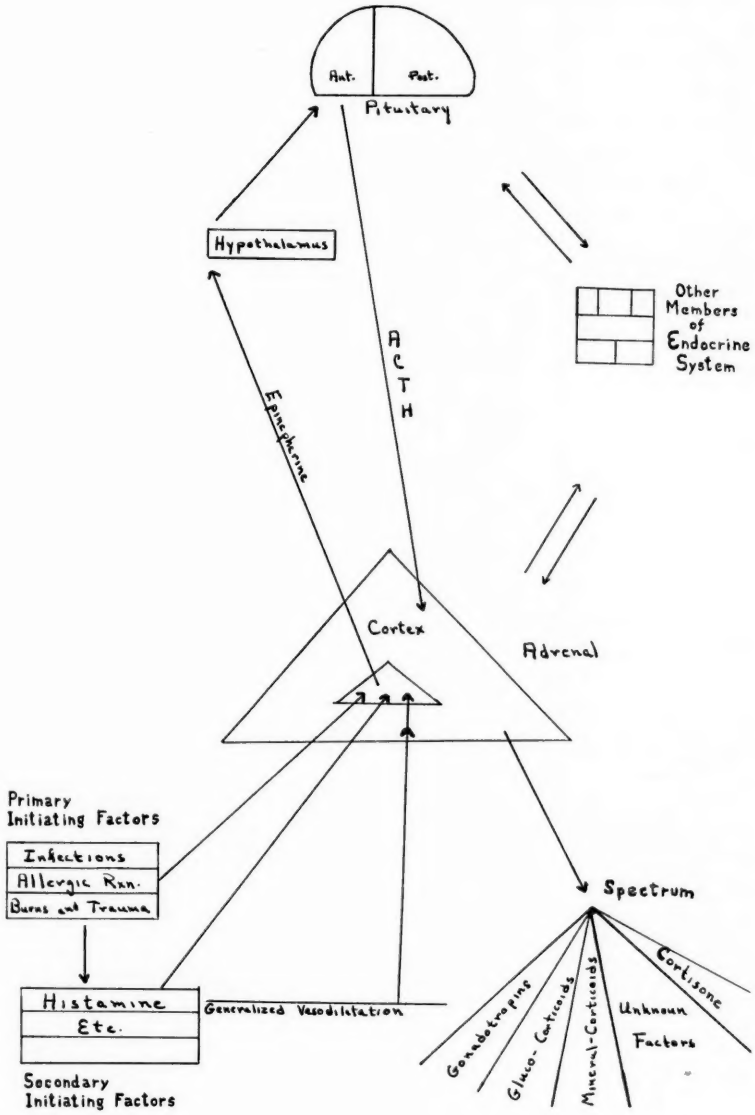

Fig. 5. The place of histamine in the "stress" phenomenon.

(steroids) which are quite similar in structure. In general, it is quite probable that when a therapeutic agent is more fully understood from the time of its chemical inception to its clinical application, a basic though not total clinical prediction will be made from its chemical structure.

SUMMARY

1. Antihistamines were of no value in the treatment of this syndrome.

2. Histamine evoked a favorable clinical response in this disease without materially altering the red cell count or hemoglobin.

3. Neither cortisone nor ACTH was able to stop the intravascular hemolysis, once it occurred.

4. With histamine followed by cortisone and ACTH therapy we were able to elicit a normal Thorn test.

5. ACTH and cortisone could not prevent the recurrence of the hemolysis, but in the periods free of hemolysis with ACTH and cortisone therapy the red cell count and hemoglobin rose to levels never before encountered.

6. Histamine, as we have used it, probably augments a sluggish physiochemical response to a toxic agent.

ACKNOWLEDGMENT

We should like to express our appreciation to Dr. E. F. Koster, pathologist at St. John's Hospital, for his help in the care of this patient.

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THE OVER-ALL PICTURE OF RHEUMATISM AND ARTHRITIS

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FOR purposes of this presentation, the term "rheumatism" will be used to describe those clinical conditions in which stiffness or pain in some portion of the musculoskeletal system are prominent; and the term "arthritis" will be used to describe those clinical conditions in which it is chiefly the joints which are involved by the rheumatic process.[5] Rheumatism and arthritis result from disease processes which often adversely affect the individual as a whole, although mesenchymal tissues seem to be principally involved.[24] Many diverse noxious agents, acting singly or in any combination or sequence, may cause a variety of rheumatic and arthritic syndromes.

Theoretically, in order to treat successfully a patient who has rheumatism or arthritis, the etiologic agent should be identified and eliminated, and tissue repair should be accelerated to neutralize tissue damage already incurred; or the tissues should be prevented from reacting to the noxious agent through the use of ACTH or cortisone.[3,7,13,17,18,24] But in practice, often the noxious agent cannot be identified, and even if it can be identified it cannot always be eliminated; it may not be possible to accelerate tissue repair so that the deteriorative effects of the noxious agent are neutralized; and the long-term administration of ACTH or cortisone may cause such undesirable side effects that the continuous use of these endocrine substances is unwarranted.

Underlying all rheumatic and arthritic syndromes are the slowly progressive, retrograde alterations in mesenchymal tissues ascribed to the so-called "normal" aging process. Detailed gross and microscopic studies of so-called "normal" knee joints indicate that deteriorative changes become evident in articular structures as early as the second decade of life.[1] Clinically, this deteriorative process is not often recognized in its earlier phases because usually joints are not studied by the physician unless they seem abnormal to inspection, or unless the patient has specific articular complaints. However, every general physical examination should include an accurate goniometric evaluation of joint mobility. Using a simple method of measuring mobility of a patient's joints and expressing this as a Joint Range Index, I found that joint mobility for a group of 750 unselected medical patients decreased linearly with increasing age, whether or not the patient had symptoms or signs referable to the musculoskeletal system. It was possible by administering niacinamide in therapeutic doses

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to cause measurable improvement in joint mobility at any age (without necessarily relieving the patient of whatever musculoskeletal symptoms he had).[12] (In evaluating a patient's response to therapy, one must distinguish between joint mobility and joint symptoms, since sometimes joint mobility may be improved without influencing musculoskeletal symptoms, and sometimes such symptoms may be ameliorated without improving joint mobility. The clinical goal in the therapy of a patient who has rheumatism or arthritis should be to improve his joint mobility and to free him from whatever musculoskeletal symptoms he may have.)

The most common cause of rheumatic and arthritic syndromes is a psychogenic one. Many persons with or without clinically obvious arthritic deformities habitually exteriorize their psychic tensions through sustained regional or generalized hypertonia of somatic muscle, which may in turn give rise to musculoskeletal symptoms. These psychogenically induced symptoms can be exceedingly severe. Some patients obtain relief from symptoms when they can be taught not to exteriorize mental tensions through sustained hypertonia of somatic muscle, or when their mental tensions are lessened through directed psychotherapy or through changes in the environment.[12,26]

Another common cause of rheumatic and arthritic syndromes is the mechanical injury of musculoskeletal structures by static or dynamic activity. Muscular contraction causes stretching of muscle and connective tissue structures (including articular capsular structures) and exerts deforming pressures on articular cartilage surfaces. Voluntary muscle is capable of creating 11 kilograms of tension per square centimeter of cross-section of resting muscle.[8] The gastrocnemius and soleus muscles together create a tension of 600 pounds when a person weighing 150 pounds walks at a moderate speed. Mechanical forces acting on musculoskeletal structures may be sufficiently great to cause a post-traumatic rheumatic and arthritic syndrome. In general, the more severe and the more prolonged the mechanical trauma, the more severe the post-traumatic syndrome is. In general, the more deteriorated the musculoskeletal structures are, the less mechanical injury it takes to produce the post-traumatic rheumatic and arthritic syndromes.[12]

Another common cause of rheumatic and arthritic syndromes is allergy. Inhalant allergies rarely cause musculoskeletal troubles. The parenteral administration of foreign protein such as horse serum, or of drugs such as penicillin, may give rise to allergic rheumatism and arthritis. In susceptible individuals oral medications, particularly penicillin, can cause allergic rheumatism and arthritis.[10] It may be that allergic rheumatic and arthritic syndromes following penicillin therapy represent the combined effects of bacterial and penicillin allergies.

Bacterial allergies seem to be responsible for certain rheumatic and arthritic syndromes.[6,23] In susceptible individuals, infections with the

Group A hemolytic streptococcus may be followed by rheumatic fever. Autosensitization of the patient to his own mesenchymal tissue proteins may increase the severity of his rheumatic syndrome.[14]

Occasionally, there is dramatic relief of rheumatism and arthritis when a focus of infection is surgically or medically eradicated. Sometimes, desensitization with autogenous or stock bacterial vaccine seems to free the patient from rheumatic or arthritic discomfort. Perhaps this improvement results from stimulation of the patient's immune mechanism and from the indirect increase of endogenous corticoid secretions in response to foreign protein. The beneficial effects of properly administered histamine upon musculoskeletal disease may in part result from improved peripheral circulation, from modification in histidine metabolism, or from increased adrenal corticoid secretion.[9,20]

Although food allergies are very common, it is only in certain cases that they cause allergic musculosketal symptoms.[12,15,23,27] Some of the difficulties in making the diagnosis of food-produced allergic rheumatism and arthritis arise from preconceptions about the nature of food allergy and from the unwarranted belief that skin testing has a high degree of specificity in disclosing offending foods.[19,22,25]

Severe fixed food allergies are rare compared to variable food allergies in which tolerance to offending foods changes from time to time as a result of known (and unknown) factors, e.g., the amount of the food eaten at any one time, frequency of ingestion of the food, endocrine status of the individual (including accentuation of sensitivity premenstrually), environmental temperature, concomitant inhalant allergies. Also, emotional factors frequently modify the extent and severity of allergenic food reactions.[2,12,16,26]

When an offending food material is eaten intermittently in amounts which are threshold for the production of rheumatic and arthritic syndromes, there is little difficulty in identifying the food. However, when a patient eats threshold amounts of an offending food daily, he develops a steady state of allergic reaction—the masked allergy described by Rinkel. A physician must know that such a steady state of allergic reaction can exist. He must know which food offenders commonly cause rheumatic and arthritic syndromes, and be prepared to recognize also uncommon offenders. The patient must cooperate with the physician in attempting to identify the offending food. The manner in which the food-symptom diary is used in identifying offending foods is described in detail elsewhere.[12] Other methods may be of value, e.g., elimination diets[21] and the specific food testing of Rinkel and others.[19] But slavish dependence on skin testing as the sole method of detecting food allergies has been responsible more than any other factor for the erroneous belief that food allergies rarely cause clinically significant rheumatism and arthritis.

When a patient is rendered symptom-free from his rheumatic and

arthritic symptoms by the elimination of an offending food, he must realize that he can become sensitized to some other food which can cause a recurrence of allergic rheumatism and arthritis. This means re-study to identify new offenders and rearrangement of his diet so that it will be nutritionally adequate. The rotary diet is extremely valuable in maintaining many patients free from allergic symptoms once the principal offending foods have been eliminated from the diet.

Antihistamines have not been especially useful in the treatment of allergic rheumatism and arthritis, although Perazil has been said to be of use in the treatment of intermittent hydroarthrosis.

The study and treatment of a patient who has rheumatism and arthritis is never easy; it is always time-consuming. The allergist who attempts to study and treat such a patient must be willing and able to manage many aspects of the patient's problems, using the methods of the allergist, internist, orthopedist, psychiatrist, physiatrist, and nutritionist—in short, whatever methods can be used advantageously.

The physician must be skilled in differential diagnosis. For example, unsuspected acute leukemia or miliary tuberculosis may simulate acute rheumatic fever clinically. Hyperthyroidism may be associated with troublesome musculoskeletal symptoms. On the other hand, hypothyroidism also may be associated with the same type of symptoms. In the former, thyroidectomy or its equivalent might be indicated; in the latter, thyroid substance should be administered.[4]

Usually, multiple etiologic factors acting concurrently are responsible for a patient's rheumatic and arthritic syndromes, and all these factors should be treated successfully if the patient is to feel well. For example, a given patient may experience partial improvement in his musculoskeletal symptoms when his allergies are properly treated, and when he receives in addition effective psychotherapy. But he will become symptom-free only when he receives, in addition to allergic therapy and psychotherapy, nutritional therapy including niacinamide, which improves his nutritional status,[11,12] and thyroid therapy, which elevates his basal metabolism to the normal range. Thus, therapy should be directed so that one subtracts successfully and successively the musculoskeletal syndromes resulting from one recognized etiology, and then from another, and then another, until ultimately the patient has been helped to feel as well as he possibly can in the year 1951.

But we must remember that treatment of such a patient must be dynamic and adapted to his changing clinical requirements. Even though he has been freed of musculoskeletal symptoms, he can at any time have a recurrence of these symptoms if he eats allergenic foods, if he develops an unresolved emotional conflict, if he discontinues niacinamide therapy, and if he again lapses into hypothyroidism as a result of discontinuing his

thyroid medication. Also, he may develop symptoms from other causes previously enumerated.

Thus, rheumatism and arthritis are dynamic syndromes. Even when it has been possible to restore full joint mobility to a patient, and to render him free from musculoskeletal symptoms, he can have recurrences of musculoskeletal troubles from time to time, from the original causes or from new ones. He should be educated to understand the dynamic nature of rheumatism and arthritis so that he can cooperate continuously with his physician in a long-range program of therapy.

SUMMARY AND CONCLUSIONS

Differential diagnosis of the multiple dynamic factors which can produce a patient's rheumatism and arthritis, and treatment of such a patient, are complicated and time-consuming. Some factors which can contribute in different ways at one time or another to the production of bodily changes diagnosed as rheumatism and arthritis are: the "normal" aging process, inferior tissue nutrition, emotional disorders, mechanical injury to musculoskeletal structures, endocrine gland malfunction, and allergies (particularly to foods, bacteria and drugs).

Each factor contributing to a patient's musculoskeletal troubles must be correctly diagnosed if treatment is to be successful. For example, if a patient has rheumatism and arthritis caused by habitual excessive contraction of his muscles when he is emotionally disturbed, then appropriate psychiatric treatment which helps him resolve his emotional conflicts often frees him of musculoskeletal discomfort. If food allergy is responsible for musculoskeletal discomfort, then proper identification of offending foods and their removal from his diet gives him relief. But if his musculoskeletal troubles are caused by psychological and allergic factors acting simultaneously, then successful psychotherapy alone will correct only a portion of the patient's difficulties; he will feel well only when both his psychiatric and allergic problems are successfully managed.

If diagnosis of rheumatic and arthritic disorders is to be correct, and if treatment is to be successful, it requires on the part of the physician expert knowledge of many specialized fields of medicine, and on the part of the patient intelligent cooperation with his physician, often for long periods of time.

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540 Brooklawn Avenue

ANTIRAGWEED COURT

A court was established this last summer in Chicago, Illinois, to specialize in violations of the antiragweed ordinance. The court operated on a full-time basis during the ragweed season and will be resumed next year.

Heavy fines were levied against property owners failing to cut the weeds on their property. By the time the season was in full swing some 2,000 complaints were on file.

THE IDENTIFICATION OF SPECIFIC ALLERGENS IN BACTERIAL ALLERGY AND THEIR USE IN DESENSITIZATION

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A METHOD for identifying the specific bacterial allergens in various allergic conditions was described earlier in this journal.[1,5,6,7] In this paper an analysis will be made of the results obtained in testing 441 individuals and in treating the 327 of these who had positive tests.

Of the 441 tested, forty were apparently healthy and normal. Their tests were uniformly negative. Negative results also were obtained for the tests of thirty patients suffering from diseases thought or known to have no possible connection with bacterial allergy.

The remaining 371 patients were tested either because bacterial allergy was suspected or because they had allergic manifestations whose causes were not revealed by other tests. Of these 327 tested postitive.

TECHNIQUE

Since test and therapy have been fully described in papers,[1-7] they need be only outlined here. White cells from the patient's blood are cultured, then bathed for seventeen hours in the filtrates of pure cultures of the different bacteria for which we wish to test. Routinely we employ 125 different strains. The percentage of cells which have been destroyed during their seventeen hours' exposure to an allergen represents the degree of the patient's sensitivity to that strain.

Desensitization generally is begun with a skin test using 0.05 cc of a 1:1,000,000 dilution of the filtrate, or a filtrate mixture if the patient is sensitive to more than one. Inoculations, given every three or four days, are stepped up gradually, first by volume, .05 cc each time until a maximum of 1 cc is reached, then by strength, the filtrates in dilution being increased tenfold each time, sometimes to full strength.

Careful evaluation of the patient's progress every four months is routine.

RESULTS

In general, the typical bacterial allergy case shows little or no improvement for the first three months but then begins to improve rather rapidly. At the routine check, after the fourth month, the patient is likely to show more improvement than the clinical findings might indicate. The sensitization tests are less positive, as a rule, but the patients usually report a disproportionate change in subjective symptoms: "feel ever so much better," "get less fatigued," "feel definitely encouraged."

In our four years, among the 202 patients who have already completed

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their desensitization schedule, 150 have become entirely symptom free and negative to all tests, some of them before they reached the 1:10,000 dilution. Half of this group have been maintained on injections of maximal tolerance every two or three weeks. The other half were discharged from treatment. Both groups are retested fairly regularly and, so far, the untreated have been doing just as well, in all respects, as those receiving continued treatment.

Other patients may become symptom free without achieving completely negative tests. These patients are always continued on maintenance injections of maximal tolerance. Many do not tolerate stronger than 1:1,000 dilution. In general, the more chronic and severe the symptoms have been, the longer the process of desensitization takes, and the greater the probability that some sensitivity will persist.

We tried discontinuing treatment on half of those patients whose symptoms had disappeared but whose white cells continued to indicate some slight sensitivity on the filtrate test. In most cases their symptoms began to recur within a few months, and desensitization had to be resumed.

Obviously the cells, not the symptoms, provide the true gauge of sensitivity.

Of all patients treated, only 3.8 per cent failed completely to respond satisfactorily.

DISCUSSION: DISEASES

Bacterial allergy is an important part of the work of every allergist, and the index of suspicion of each of us should be kept high.

Which diseases should be tested?

Every rheumatic fever and rheumatoid arthritis patient we have tested so far has been positive. So far every "id" infection case (bacterids) has been also. So have all of our twenty-five sinusitis cases (all of which, incidentally, had very positive histories of infection).

Both positives and negatives were yielded by bronchial asthma, recurrent iritis, recurrent uveitis, and rhinitis. In this group more than 50 per cent showed bacterial hypersensitivity, and a large number had mixed allergies—both bacterial allergy and atopy.

Occasional positives were found in psoriasis, herpes labialis, urticaria, acne vulgaris, bronchiectasis, chronic bronchitis, migraine, paroxysmal tachycardia, and vague gastrointestinal disorders.

Neither to be overrated nor ignored were positive tests in cases of Marie-Strümpell disease, gonorrheal arthritis, pigmented villo nodular synovitis, periarteritis nodosa, acute disseminated and chronic lupus erythematosus, Schüller-Christian disease, chilitis, recurrent erysipiloid eruptions, acute glomerulonephritis, pruritus vulvae, chronic prostatitis, progressive muscular dystrophy, and multiple sclerosis. Although we got excellent results in the specific treatment of some of these, we prefer to let them stand as interesting observations. We have had too few cases to evaluate

the significance; at this time all we can say is that they give positive cell culture tests.

DIAGNOSIS

Bacterial allergy, in some instances, may be not only suspected but diagnosed almost with certainty even before the tests are made. For example, if a sinusitis patient had his first attack following a winter cold, with temperature, and thereafter attacks became more frequent, perhaps worse on damp days; if there is a thick, yellowish postnasal drip, hazy frontal sinuses, congested turbinates (not necessarily livid)—in the presence of such a history it is almost certain that the case is one of bacterial allergy.

Sinusitis, asthma, rheumatic fever, and arthritis patients not only have many colds and sore throats but also pyorrhea in many cases.

Other groups have a history of severe infective processes just preceding their symptoms. In several cases we found that the sensitizing agent had been in typhoid fever or a gall bladder disease. *Since the white cells react to the filtrate only after sensitization, not during the course of an infection,* our test is valuable to determine whether an allergic reaction has developed during exposure to the infection.

RESPONSE TO THERAPY

Cases differ widely in their response to desensitization. In the typical case of coryza with sinus symptoms of long standing, desensitization results in fewer colds, the secretion is thinner and often absent for days at a time, and the postnasal drip is much less bothersome.

Bacterid infections respond dramatically, and often are apparently cured at the end of 120 days.

Rheumatic fever cases, at the end of the fourth month of desensitization, usually have normal sedimentation rates of their blood cells, no tachycardia, normal electrocardiographic PR intervals, and are asymptomatic.

Rheumatoid arthritis, especially if of long standing, is slow to respond, and patients also should be warned that their symptoms may appear to become worse for a short time after treatment begins. By the end of four months, however, they feel better generally, have joint pains only on their bad days, and exhibit better motility and less edema. Their joints still will be stiff when they arise in the morning, and as a rule the objective signs are unchanged.

DEVELOPMENT OF NEW SENSITIVITIES

In three cases, patients were found to have developed a new bacterial sensitivity while being treated for an established one. Allergic manifestations having recurred, retests were made; but the white cells demonstrated that desensitization to the allergens first identified was progressing normally. Therefore, the patient was retested for the other filtrates, and in each instance turned up a positive reaction to an allergen to which he had not been positive originally, i.e., a few months earlier.

Such new sensitivities are as amenable to treatment as the old. An example was a patient who had been suffering from a severe recurrent pansinusitis and upper respiratory infections before desensitization was begun. She was getting brilliant results—but when a pneumonitis set in, her original symptoms returned with visual disturbances added. When retested to the filtrates with which she was being treated, the cells were now almost completely negative, but two other strains, which formerly were negative, now gave strongly positive reactions. Adding injections of these new strains eliminated the symptoms.

Unfortunately, virtually anyone with bacterial allergy has depressed resistance to infections, especially in childhood. Perhaps in consequence, on the first test most patients are found to be sensitive to two or more filtrates. As one might expect, it is apparently possible for an individual already sensitized to one strain to develop new sensitivities at any time upon sufficient exposure. Once desensitization has begun, however, it is the exception rather than the rule for an individual to acquire additional sensitivities.

As yet we have no record of a patient acquiring new sensitivities, or becoming resensitized to his original strains, after the desensitization program has been completed.

CONCOMITANT ATOPIC AND BACTERIAL ALLERGIES

Mixed allergies—combinations of bacterial allergy with some other type, such as a drug sensitivity or an atopy—are likely to be frustrating cases when one but not the other allergy is recognized and treated. After full diagnosis and treatment for both simultaneously, gratifying progress is made. It cannot be emphasized too strongly that the individual who has had hay fever and asthma over many years may develop a bacterial type of allergy also. When a case of atopic allergy is not responding satisfactorily, a concomitant bacterial allergy must be suspected.

A large proportion of our 327 cases had atopic as well as bacterial allergies; most of these had had repeated upper respiratory diseases.

Typical of stubborn mixed allergy was the thirty-year-old woman asthmatic patient with rhinitis and hay fever. For years she had taken injections for hay fever and had strictly avoided the inhalants to which she was sensitive. But each season she had some hay fever and for several summers had had to be hospitalized for asthma. When therapy for her bacterial allergies was instituted, she became asymptomatic within two months and enjoyed her first summer in which the hay fever stayed under control.

SUMMARY

1. The validity of the bacterial sensitivity tests and the therapy technique has now been thoroughly established, with no record to date of either false positives or false negatives. Furthermore, originally positive

patients improve to the point where they test negative and often are entirely symptom free.

2. The test is invaluable as a diagnostic tool in establishing the cause of symptoms and in indicating specific therapy.

3. In rheumatoid arthritis, rheumatic fever, "id" infections, and certain other diseases, tests for bacterial allergy should always be run. In others they should be used whenever the history is of a bacterial type. Finally, the tests sometimes give gratifying results when run as a last resort.

4. Patients having atopic allergies resistant to therapy should always be suspected of having concomitant bacterial allergy and should be tested accordingly.

5. Diseases vary in their responsiveness, but in all cases the sensitivity of the cells seems to respond more slowly than the symptoms. In no case should a patient be discharged until his cells are negative to all strains; otherwise his symptoms probably will return.

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580 Doctors Building

CUTANEOUS MANIFESTATIONS OF DRUG HYPERSENSITIVITY

Your attention is called to the special article by the well-known allergy specialists, Doctors Alex S. and Sidney Friedlaender, Departments of Microbiology and Medicine, Wayne University College of Medicine, Detroit, Michigan, which will appear in the forthcoming March, 1952, issue of *Quarterly Review of Allergy and Applied Immunology*. It is a comprehensive review of the subject of drug hypersensitiveness, exemplifying the authors' vast experiences with it. This authoritative article covers immunologic considerations, morphology, and specific drugs causing cutaneous eruptions, including the barbiturates, iodides and bromides, arsenicals, gold salts, sulfonamides, antibiotics, and ACTH and cortisone, as well as treatment. The bibliography is complete, and four tables are included.

COMPARATIVE EFFECTIVENESS OF ORAL PROCAINE AND TEDRAL IN ALLERGIC CONDITIONS

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THE treatment of allergic conditions often presents a difficult problem in spite of the wide variety of drugs available for treatment. While desensitization may be the method of choice, it is not always practical or effective.

Procaine hydrochloride by the intravenous route has been found to be effective in certain allergic conditions. In this country its use has been limited mainly to the treatment of cases of serum sickness of diverse etiology.

In 1946, State and Wangensteen[9] treated twenty-seven cases of serum sickness and urticaria due to various agents with good results in twenty of them. There was one case of chronic asthma among them. This case did not respond to intravenous procaine. Applebaum, Abraham and Sinton[1] reported dramatic relief following intravenous procaine in a case of serum sickness following the injection of tetanus antitoxin. Dressler and Dwork[4] treated a case with a serum-sickness type of reaction following penicillin with similar spectacular results. Four cases of serum-like reactions to penicillin were reported by Cohen and Kaufman.[2] Of these, two cases (50 per cent) responded favorably to procaine intravenously.

Waldbott[10] has attempted to temper the enthusiasm for the use of intravenous procaine with a reminder that sensitivities to procaine and other related drugs are not uncommon. He reports one case of a near fatality where the patient went into severe shock immediately following the intravenous administration of 0.5 gm of procaine in 250 cc of saline. However, fatalities from procaine are rare. Mayer,[6] in 1924, reviewed the literature on the use of procaine as a local anesthetic and found only two deaths reported.

Interest has recently been focused on the use of procaine orally for the treatment of bronchial asthma, as a result of the report of a case by Schapiro and Sadove[7] who kept an eighteen-year-old girl with severe intractable asthma symptom-free for many months on the continued administration of procaine by mouth. These authors further stated that, although procaine had been used abroad intravenously and in the form of stellate ganglion blocks for the treatment of asthma with considerable success, they could find no reference in the literature to the use of procaine by mouth. The case they report is all the more interesting because a prior attempt at

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intravenous procaine therapy had led to an immediate severe sensitivity reaction, characterized by sudden respiratory arrest followed by intense dyspnea, marked flushing of the face, and extreme nervousness. The authors make no attempt to explain the mode of action of procaine given by mouth.

PHARMACOLOGY AND PHYSIOLOGICAL ACTION OF PROCAINE

Procaine is the diethylamino ester of para-aminobenzoic acid and is about one fourth as toxic as cocaine.[3] It is destroyed mainly by the liver, where it is broken down to para-aminobenzoic acid and diethylaminoethanol. These end products are excreted by the kidneys.

An excellent review of the pharmacology of procaine is given by State and Wangensteen,[9] who further state some theories as to its action in allergic conditions. Procaine affects all living cells, but its main action is on the nerve fibers, where it produces an attenuation in the conduction of impulses. It also has a curare-like action in reducing the amount of acetylcholine produced at the myoneural junction and has a depressant effect on the acetylcholine already produced. Procaine also has the property of potentiating the response of sympathetically innervated organs to epinephrine, to sympathin, and to sympathetic nerve stimulation.

The mode of action of procaine in allergic conditions is unknown. The following theories, which have been proposed, are purely conjectural:

1. Direct action on cells: The relief of myalgia and arthralgia in serum sickness can best be explained by the anesthetizing action of procaine on the nerve fibers carrying pain stimuli from the muscles and joints. There is also a direct action on the endothelium of the arterioles and capillaries resulting in vasodilatation.
2. Antihistaminic action: There is absolutely no proof that procaine has any antihistaminic properties.
3. Antiacetylcholine action: Some of the manifestations of serum sickness, particularly the spreading flare about the wheal, are probably due to the liberation of acetylcholine at the nerve fiber endings of the terminal arterioles, and their disappearance on the injection of procaine might be due to its antiacetylcholine action.
4. Epinephrine potentiating action of procaine: This action may help the epinephrine secreted by the body to combat various allergic manifestations.

EXPERIMENTAL DRUGS

On the basis of these observations, it was thought that oral procaine merited further study. For comparative purposes, it was decided to use Tedral,®* an antiasthmatic preparation with which we have had considerable previous experience.

*Tedral® formula: theophylline, 2 gr; ephedrine, 3/8 gr; phenobarbital, 1/8 gr.

TABLE I

Diagnosis	Treatment	Total No. of Cases	Improved		Unimproved		Statistical Significance of Results	
			No.	%	No.	%	X^2	P
Bronchial asthma	Procaine	33	7	21	26	79	8.8*	Less than .01
	Tedral	20	14	70	6	30	40.9*	Less than .01
Hay fever Vasomotor rhinitis	Procaine	18	3	17	15	83	3.61	Less than .10
	Procaine	15	1	7	14	93	0.03	—
	Tedral	10	1	10	9	90	0.2	—
Urticaria	Procaine	5	1	20	4	80	0.8	Less than .50
	Tedral	2	2				21.7*	Less than .01
Allergic bronchitis	Procaine	1	0		1			
Atopic dermatitis	Procaine	2	0		2			
	Tedral	1	0		1			
Allergy	Placebos	59	1		58			

*Statistically significant results (10). Mr. Neil R. Stasilli, Research Department, Chilcott Laboratories, kindly compiled the statistical information:

X^2—An X^2 value greater than 3.8 is considered significant, on the basis of probability or chance that value or any larger one indicates that the treatment was effective.

X^2 was derived from the following formula: $X^2 + \frac{[(ad-bc)-\frac{1}{2}(a+b+c+d)]^2(a+b+c+d)}{(a+b)\quad(c+d)\quad(a+c)\quad(b+d)}$

a—Number of cases treated and improved.
b—Number of cases treated and unimproved.
c—Number of cases treated with placebo and improved.
d—Number of cases treated with placebo and unimproved.
P—Where P is less than .01, it indicates that the odds are at least 99 to 1 in favor of the remedy having had a beneficial effect.

On the basis of the X^2 test the following can be stated:
1. Procaine was significantly useful in treating bronchial asthma.
2. Tedral was significantly useful in treating bronchial asthma.
3. Procaine had doubtful significance in the treatment of hay fever.
4. Procaine was of no value in the treatment of vasomotor rhinitis.
5. Tedral was of no value in the treatment of vasomotor rhinitis.
6. In the treatment of urticaria there were not enough trials for any conclusions to be drawn.

The beneficial effect of Tedral in relieving the symptoms of the average case of bronchial asthma is well known and accepted by allergists. The use of Tedral for asthma has also become common among general practitioners.[8]

Experimental preparations containing procaine to be used in the study consisted of the following formulas:

*CH-25***
Procaine hydrochloride.....300 mg
Ascorbic acid.....100 mg

*CH-33***
Procaine hydrochloride.....300 mg
Placebos identical in appearance to CH-25 and CH-33 were also provided.

CLINICAL MATERIAL

Patients coming to the allergy clinic of the Beth-El Hospital, with the usual variety of allergic complaints, were chosen for study. Cases of bronchial asthma, atopic dermatitis, seasonal rhinitis, vasomotor rhinitis, and urticaria were included in the series. Forty-one females and thirty-two males, ranging in age from three and one-half years to sixty-nine years,

**Experimental preparations CH-25 and CH-33 and Tedral plain and enteric coated were supplied through the courtesy of Dr. William T. Strauss, Chilcott Laboratories, Division of The Maltine Company, Morris Plains, New Jersey.

TABLE II

	Total Number of Patients	Side Effects			
		Severe	Mild	Total	Per Cent
Procaine	74	13	7	20	27
Tedral plain	28	3	1	4	14
Tedral enteric coated	26	5	4	9	34
Placebos	59	4	7	11	18

were included in the study. Since the response to Tedral in bronchial asthma was predictable, based on previous experience, it was decided to place the patients on the experimental preparations and placebos prior to the use of Tedral. Patients were asked to return to the clinic at weekly intervals. Each was given a questionnaire to fill in.

RESULTS

Results of the comparative study between procaine and Tedral are shown in Table I.

In general, response and relief of symptoms were not encouraging with CH-25 and CH-33. Based on our experience, there was no significant difference in effect between procaine and ascorbic acid and procaine alone. For purposes of recording results, therefore, we have listed the two together. Twenty-one per cent of thirty-three patients received relief from procaine, but on the basis of probability, it is shown to be of some value.

Tedral plain gave excellent results in 70 per cent of the patients with bronchial asthma, approximately the anticipated finding. Tedral enteric coated is designed to give delayed relief (four hours) and may be taken simultaneously with a plain Tedral tablet. Several patients reported, however, that Tedral enteric coated gave them relief within one half to one hour; and in one patient the relief lasted for an entire day. Since the therapeutic ingredients of Tedral plain and enteric coated are identical, psychic factors are probably the explanation for the claim and for the fact that a few patients reported good effects with one form and not the other.

While the previous investigators reported virtually no side effects with oral procaine, the incidence was high in this series.

Table II gives the incidence of side effects observed with the drugs used.

Types of side effects observed are listed in Table III. With procaine, headache, dizziness, nausea, and cramps were most frequently observed; while with Tedral, cardiac palpitation (probably due to ephedrine) and weakness were the most frequent complaints.

DISCUSSION

An attempt has been made to evaluate a new drug therapy, procaine by oral administration, in the symptomatic treatment of allergic conditions, with particular attention to the effect in bronchial asthma.

In recent years many new drugs have come to the forefront in the

TABLE III. SIDE EFFECTS

	Procaine		Tedral Plain		Tedral Enteric Coated		Placebo	
	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild
Headache	4	5	1	—	1	—	1	2
Weakness	—	4	—	1	—	1	—	1
Dizziness	—	6	—	1	—	1	2	1
Nervousness	—	2	—	—	—	2	—	1
Diarrhea	—	1	—	—	—	—	—	1
Nausea	5	3	—	—	—	—	1	1
Visual disturbance	2	—	—	—	—	—	—	—
Abdominal cramps	5	—	—	—	—	—	—	—
Constipation	—	2	—	—	—	—	—	2
Vomiting	3	—	—	—	1	1	1	—
Urinary frequency	—	1	—	—	—	—	—	—
Drowsiness	1	—	—	—	—	—	—	—
Flushing	—	1	—	—	—	—	—	—
Heartburn	1	—	—	—	1	—	1	2
Tiredness	—	—	—	—	1	—	—	—
Itching of skin	—	—	1	—	—	—	—	—
Cardiac palpitation	—	—	1	—	1	1	—	—
Burning in stomach	—	—	1	—	1	—	—	—
Belching	—	—	1	—	1	—	—	—

therapy of various manifestations of allergic disease. Many of these have fallen by the wayside, but some of them have become a valuable addition to our chest of therapeutic tools for the treatment or control of allergic symptoms. In the latter group are the antihistaminic drugs for the symptomatic treatment of hay fever and acute urticaria, intravenous procaine for the treatment of serum sickness due to various causes, and aminophylline and the various epinephrine-like compounds in the treatment of bronchial asthma. Other allergic conditions, such as chronic urticaria and perennial allergic rhinitis, have remained singularly resistant to symptomatic therapy with these newer drugs.

Evaluation of any new drug or therapeutic method in allergic conditions is fraught with many pitfalls, since there are many factors affecting these conditions which are difficult to control. Among these may be mentioned such factors as spontaneous remissions, which occur frequently in allergic states; fluctuating environmental influences; and, of great importance in many cases, psychogenic factors.

One of the greatest difficulties we faced in our investigation was getting our patients to fill out properly the questionnaires given to them on their weekly visit to the clinic. In all cases the information on the questionnaire had to be supplemented by close personal questioning in order to determine as accurately as possible the effect of the medication given.

Our greatest interest was in the effect of oral procaine on the symptoms of bronchial asthma. Our results here were not particularly encouraging. Only 21 per cent of our asthmatic patients showed 50 per cent or more improvement as compared with similar improvement shown by 70 per cent of the patients who received Tedral, a drug which has long been a standby in the treatment of the symptoms of bronchial asthma and the effectiveness of which has been definitely established. Nevertheless, it is our feeling that in spite of the poor results with procaine, the drug may be effective in an

occasional case that does not respond to other medication. The results in vasomotor rhinitis were uniformly poor with both procaine and Tedral. In hay fever similar disappointing results were obtained with procaine. No Tedral was given to this group because their symptoms had abated spontaneously by the time they could be given a trial with this drug.

It is interesting to note the large number of patients who experienced side reactions from the administration of the placebo medication. Eighteen per cent of this group experienced reactions of varying severity. One patient had such bad side effects that she had to discontinue the medication after two days. This may indicate the importance of psychogenic factors in patients with allergic manifestations.

From this study it is our opinion that the use of procaine in the treatment of bronchial asthma and other allergies did not give satisfactory results in a sufficient percentage of our cases. The results with Tedral confirmed our previous experiences that this combination of drugs was a satisfactory therapeutic agent in the treatment of bronchial asthma.

SUMMARY

1. Procaine hydrochloride, procaine hydrochloride and ascorbic acid, and Tedral were given comparatively to a series of patients with bronchial asthma, hay fever, vasomotor rhinitis, urticaria, and atopic dermatitis.

2. Oral procaine therapy was found to be of little value in the treatment of bronchial asthma, especially when compared with an ephedrine-theophylline combination like Tedral.

3. Oral procaine was likewise of no value in the treatment of other allergic diseases such as hay fever, vasomotor rhinitis, urticaria, and atopic dermatitis.

4. There was a high incidence of side reactions with oral procaine therapy. The addition of ascorbic acid did not materially alter this high incidence of side reactions nor add to its therapeutic effectiveness.

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881 Park Place
(Doctor Markow)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

COLLEGE MEMBERSHIP

What Membership Means: To advance and maintain the highest possible standards in allergy; to work for certification of physicians specializing in allergy; to participate in the Annual Meetings of the College; to contribute to ANNALS OF ALLERGY; to promote fellowship; to support the College financially; to serve on committees.

The Founders, when setting forth the aims of the College, purposely defined clear objectives for those who comprise its membership. Ever since the society was founded in 1942, the officers have made sincere efforts to impartially further its aims, realizing that honors come only through work and sacrifice.

When names were proposed for membership by those interested in the welfare of the College, it was their intention that physicians accepted for membership should adhere to its precepts—to advance the laboratory and clinical knowledge of allergy by conscientious practice and research, to participate in the regular Congresses of the College, and in every way possible to promote good fellowship and interest.

Members have the honor of belonging to the largest allergy society in the world, whose roster comprises a majority of outstanding scientists and allergists in North and South America; they enjoy all the rights and privileges of such a society. If you as a member are willing to work and if you signify that intention to the officers by word or precept, you can serve on important committees and function in many other College activities.

What Membership Does Not Mean: To join so as to be sure it is only to your personal advantage to do so; to receive a diploma to show your patients; to be indifferent to all College activities; occasionally, infrequently, or never to attend College Annual Meetings; to be disgruntled and envious of honors received by those members who conscientiously strive and make sacrifices of time and money for a College which has done more during its existence to stimulate interest in allergy and related fields throughout the world than any other group.

Where Do You Stand?

Kardex records show the activities in the College of every member, including his attendance at meetings or instructional courses, participation in programs, service on committees, research activities, and publications. It is incredible but true that some members who have been active Fellows of the College for nearly ten years have never attended a meeting, have

never submitted a paper to the ANNALS for publication, and in no other way have shown interest in College activities. World War II, of course, has been an unsettling influence. Sufficient time has now elapsed, however, that better co-operation can reasonably be expected from this group. It is earnestly hoped that these inactive Fellows will in the future co-operate in promoting good fellowship and making our meetings even more successful.

Article 4, Section 2 of the By Laws reads:

"The state of Active Fellowship shall lapse by reason of absence from three (3) successive meetings, unless reason therefor, acceptable to the Board of Regents, is given."

This provision has never been used to deprive a Fellow of his College status. It is, however, on the agenda for the Board of Regents meeting at Pittsburgh in April, 1952. The attendance records and College activities of every Fellow will come up for scrutiny.

The College meetings have been moved to early spring in order to avoid weather conditions not conducive to travel. Very few have been prevented from attending through illness.

The College now has such an outstanding roster of prominent scientists and allergists who are very active in College affairs that quality, as portrayed by interest and achievement, is to be preferred to quantity, as evidenced by a huge membership.

We sincerely appeal to those who are indifferent to the College activities to commence this new year with a resolution henceforth to be "Regular Fellows."

ALLERGY TO DIPHTHERIA TOXOID

The observation of an attack of bronchial asthma after a booster dose of diphtheria toxoid induced W. J. Kuhns and his colleagues* to start a systematic investigation of allergic phenomena following immunization with this antigen. In this particular case—a child with the stigmata of allergic reactivity in both his personal and his family history—no precipitating (flocculating) antibody was found in the serum, although the test in rabbit skin indicated considerable neutralizing power for diphtheria toxin. It appeared, therefore, that an antibody of the nonprecipitating type was present in this child. A passive transfer test with this serum showed an immediate reaction with diphtheria toxoid at the sensitized sites.

The follow-up of this first observation in numerous volunteers

*Kuhns, W. J.; Lawrence, H. S., and Pappenheimer, A. M., Jr.: Federation Proc., 10:413, 1951. Also papers presented by the senior author at the December meeting of the Section on Microbiology of the New York Academy of Medicine (1951) and at the meeting of the New York City Branch, Society of American Bacteriologists. January 3, 1952.

showed that a human being may produce at an individually greatly varying degree three different kinds of antibody: namely,

1. The classical antitoxin, which neutralizes toxin (as demonstrated in rabbit's skin), precipitates diphtheria toxin *in vitro*, fixes complement with this antigen, and causes an immediate wheal-and-flare reaction, if toxoid is brought into a site sensitized with the serum. However, this reaction is obtainable only if the antigen is injected into the sensitized site within a period of minutes after deposition of the serum. In other words, this antibody is not "fixed" dermally.

2. A heat labile antibody, which neutralizes toxin *in vivo* but does not precipitate it *in vitro*, which does not give complement fixation reaction, and which does sensitize human skin for a matter of weeks. In other words, it behaves like the "reagin" of the common reaginic type of allergy.

3. "Blocking" (or "neutralizing") antibody, which is heat stable.

Both kinds of antibody (1 and 2) cause passive anaphylaxis in guinea pigs with diphtheria toxoid as antigen.

Many of the sensitized subjects showed direct reaction of the wheal and flare type upon intradermal injection of minute amounts of diphtheria toxoid.

For the allergist, these observations are of great interest. They open an avenue for further experimentation with an antigen which can be obtained in high purity (such as was employed in these experiments). They invite further experimentation with well-defined antigens, from which much quantitative data can be expected. As a first example of future results which can be hoped for from work of this kind, it has been shown that true allergic reactivity can be evoked by the common "immunizing" procedures, in other words, intentionally and at will.

SECTION ON ALLERGY, MEDICAL SOCIETY OF THE COUNTY OF KINGS

The next meeting of the Section on Allergy, Medical Society of the County of Kings and Academy of Medicine of Brooklyn, will be held at the Kings County Society Building, 1313 Bedford Avenue, Brooklyn, New York, on Tuesday, March 11, 1952, at 8:30 p.m.

"Clinical Aspects and Management of Drug Allergy" will be the subject of William B. Sherman, M.D., Assistant Clinical Professor of Medicine, Columbia University; Attending Physician, Roosevelt Hospital, New York; and Editor, *Journal of Allergy*.

Members of the medical profession are cordially invited. The business meeting and election of officers will follow the program.

The Editor's Page

ON THE PHARMACEUTICAL FRONT

A RATIONAL and truly scientific approach to a medical problem would emphasize diagnostic studies aimed for the discovery of the cause of the patient's condition. In this aspect of medicine, unfortunately, we have a great deal to learn. An examination of the literature shows a preponderance of papers concerned with treatment as compared to those dealing with prime causes. The patient (God bless him!) wants symptomatic relief, immediate and long-lasting and, if possible, complete. The pharmaceutical manufacturer (God bless him, too!) earns his money by furnishing the cause of such relief. For him, if one drug does not work, he tries two. If two are ineffective, the answer is three or more.

For the symptomatic relief of the so-called common cold, the American public purchased over $20,000,000 worth of antihistaminic agents to discover the truth of an old saw: it isn't what you know that does you harm, but what you know that isn't so. The total sales for the next succeeding cold season decreased to under $5,000,000. But if antihistaminic agents do not work, excepting in the allergic patients who perhaps in the first place never did have colds, perhaps a mixture of antihistaminic drugs and other medications may help both allergic and nonallergic patients who think they have or are going to have colds.

Among other treatment mixtures offered at home and abroad is Neomalene®, each capsule of which contains pyrilamine maleate (25 mg) and codeine phosphate (16 mg). Another mixture, Pyraldine®, contains in each ounce pyrilamine maleate (75 mg), dihydrocodeinone bitartrate ($^1/_6$ gr), with ammonium chloride (6 gr) and citric acid (5 gr).

Another mixture of four drugs is Dipane and Ebesal Co.®, in which we have pyrilamine maleate (25 mg), acetylsalicylic acid (3½ gr), phenacetin (2½ gr) with caffeine citrate (½ gr).

If the patient's condition cannot be improved, a little euphoria will do him no harm. In Amsalin®, he receives pyrilamine maleate (12 mg), phenylpyramine fumerate (2 mg), salicylamide (150 mg) and also d-amphetamine phosphate (1 mg).

Of course, these mixtures by no means exhaust all the possibilities. Let's take a look at Synephricol Thenfadil® in which we have the synergistic action of five drugs. A teaspoonful includes Thenfadil hydrochloride (4.0 mg), Neosynephrine hydrochloride (5.0 mg), codeine phosphate (0.7 mg), potassium guaiacol sulfonate (70.0 mg), and ammonium chloride (70.0 mg).

In Astapect®, we have a mixture of seven drugs, although, strictly speaking, the two bromides and both of the thiocyanates can each be counted

as one. In each 1 cc the patient takes ephedrine hydrochloride (0.005 Gm), codeine phosphate (0.02 Gm) with unspecified amounts of fluid extract of thyme potassium and ammonium thiocyanate with potassium and sodium bromide.

If the patient coughs, some of the new products being prescribed include Bromocodeina®, a syrup containing bromoform, codeine, aconite, and tolu. A new tablet named Codefedrine® contains codeine phosphate (0.02 Gm), ephedrine hydrochloride (0.01 Gm), caffeine (0.05 Gm), and sodium benzoate (0.05 Gm) with excipients.

A suppository named Tussicone®, available for the moment in Canada, contains this incredible mixture of drugs: namely, guaiacol acetate, sulfadiazine, sulfamerazine, ethoxytheophylline, and codeine.

Such mixtures are not limited to our Canadian friends. For asthmatic patients we at home are offered Aerolin compound®, of which each 100 cc contains cyclopentamine hydrochloride (0.5 Gm), aludrine hydrochloride (0.25 Gm), atropine sulfate (0.1 Gm), and procaine hydrochloride (0.2 Gm) in propylene glycol (80 cc) in distilled water.

Our Cuban friends are offered Pasmin® suppositories containing aminophylline (0.50 Gm), papaverine base (0.05 Gm), and phenobarbital sodium (0.02 Gm) in cocoa butter.

These are only some of the mixtures available from the corner drug store, whose owner finds himself increasingly often pouring mixtures from one bottle into another. The art of prescription writing is at as low an ebb as it can be, due, perhaps, to the fact that physicians will not bother to write prescriptions. The pharmaceutical manufacturers, under the circumstances, will furnish us with more and more factory-produced mixtures.

After all, you can't blame the boys for trying.

PROFESSOR ROBERT DOERR

As this issue goes to press, we regret exceedingly to report receiving the announcement of the death of Professor Robert Doerr of Basel, Switzerland.

Professor Doerr, a scientist of international fame, was elected an Honorary Fellow of the College on June 28, 1946, at the annual meeting at San Francisco.

His obituary and photograph will appear in the March-April issue of the ANNALS.

The officers of the College extend their sincere sympathy to his widow and family.

The First International Congress on Allergy

Zurich, Switzerland

The International Association of Allergology now takes its place in the international picture, along with the World Medical Association. Conceived through the constructive imagination of Fred W. Wittich and guided to its first meeting by his genius for organization, this society, along with other similar ones, will be a potent agent not only for the dissemination of medical knowledge but also for the promotion of international fellowship and peace.

The first meeting in Zurich, Switzerland, September 23-29, 1951, was sponsored by the Swiss Federal Council, the Canton and the City of Zurich, and by the several allergy societies of Switzerland. Dr. h. c. Ph. Etter, Swiss Minister of the Department of the Interior, was Honorary President, and Professor Dr. Ch. W. Loeffler, of the Institute of Hygiene of the University of Zurich and President of the Swiss Allergy Society, was President. Professor Dr. A. S. Grumbach, also from the Institute of Hygiene, was General Secretary, and Director A. G. Mann was Treasurer. To Dr. Grumbach and to the other members of the Committee on Organization, Professor Dr. Loeffler and Director Mann, is due the credit for the remarkable facility with which the meeting proceeded. Nothing had been omitted that could aid the speakers or that might contribute to the convenience, comfort, and pleasure of those in attendance.

Madame Grumbach headed the Ladies' Committee, which provided entertainment for the visiting ladies every day. The natural beauty for which Switzerland is renowned can be no greater than the hospitality of her people.

The social activities of the Congress were initiated by a reception in the Zurich Congress House on Sunday evening, September 23. On Tuesday at the Dolder Grand Hotel, there was an evening of entertainment, dancing, and visiting, with the wonderful food and wine for which Switzerland is famous acting as a potent catalyzer. On Thursday, the Congress was tendered a luncheon at Basel by the pharmaceutical houses of Ciba, Hoffmann-La Roche, and Sandoz. The official banquet on Friday evening was presided over by Professor Dr. Loeffler, who delivered his presidential address in German, in French, and in English. Unusual entertainment was furnished in the form of orchestral music, singing, yodeling, and a most remarkable manipulation of the Swiss flag by a flag juggler.

In addition to the official entertainment, there was opportunity for more intimate conversations over coffee or a glass of wine, by the refreshment bar near the main Congress Hall, at lunch in the Congress Hall restaurant, or at dinner in the famous restaurants of Zurich, some of them hundreds of years old.

The scientific program, which began on Monday morning and finished at noon on Saturday, consisted of 210 presentations by approximately as many authors, and encompassed the field of allergy. In the morning, general sessions were held in the Congress Hall, and papers on main topics were read, varying from thirty to forty minutes in length. In the afternoon, in small auditoriums, there were further discussions of these main topics with an opening paper of fifteen minutes, followed by several more

of ten minutes each. On Thursday, there was an excursion to Basel, with a scientific session in the morning, followed by a luncheon, and then visits to the plants of Ciba, Hoffmann-La Roche, and Sandoz. The research departments of these firms gave a remarkable demonstration of their experimental work.

To those of us old enough in medical years to remember the first years of allergy with doctors searching in a faltering manner for the first small glimmer of scientific truth, the presentations of this Congress are a miracle. There were papers on research, immunology, pharmacology, chemistry, pathology, the mechanism of sensitization, the social and economic implications of allergy and its geographic distribution, the industrial importance of allergy, the relation of bacterial antigens and of parasites to allergy, constitution and heredity, the relation to other diseases, psychosomatic factors, the effect of hypnosis on allergic disturbances, the practical diagnosis and treatment, tests and reactions, and special studies of allergic disturbances of all the various organs and systems of the body.

There was a registration of about 600 people from twenty-eight different countries—Australia, Austria, Belgium, Brazil, Canada, Ecuador, England, Finland, France, Germany, Indonesia, Israel, Italy, Lichtenstein, Mexico, Norway, Persia, Peru, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey, United States, Uruguay, and Yugoslavia. The larger number of the registrants came from France, Germany, Great Britain, Italy, Sweden, Switzerland, and the United States.

From the United States, there were seventy-eight registrants, including fifty-seven physicians, some members of the Academy, some of the College, and most, members of both. Dr. A. R. Rich of Baltimore and Dr. M. G. Bohrod of Rochester, New York, were guest speakers; twenty-one other doctors from the United States read papers. The Surgeon General of the Army, George E. Armstrong, acting through the Division of International Conferences, Department of State, selected the United States Delegation to the First International Congress on Allergy as follows:

As *chairman*—Arthur Stull, Ph.D., Pathology and Allied Sciences Division, Office of the Surgeon General, Department of the Army; as *delegates*—Arthur J. Berger, Lt. Colonel, M.C., U.S.A., Chief, Allergy and Immunology, Walter Reed General Hospital, Washington, D. C.; Milton G. Bohrod, M.D., Pathologist and Director of Laboratories, Rochester General Hospital, Rochester, New York; Joseph Harkavy, M.D., Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York; Howard Osgood, M.D., Chief, Allergy Clinics, Buffalo, New York; Arnold A. Rich, M.D., Baxley Professor of Pathology, Johns Hopkins Hospital, Baltimore, Maryland; Louis Schwartz, M.D., Acting Assistant Surgeon, Columbia Medical Annex, Washington, D. C.; and James J. Smith, M.D., Chief, Education Division, Department of Medicine and Surgery, Veterans' Administration.

Meetings of committees continued throughout the session to complete the formation of the International Association of Allergology. For the Academy, Dr. F. M. Rackemann was the voting representative; Dr. S. M. Feinberg served on the Committee on the Constitution and By Laws, and Dr. Howard Osgood, on the Committee on Nomenclature. For the College, Dr. Ethan Allan Brown was the voting representative; Dr. Fred W. Wittich served on the Committee on Constitution and By Laws, and Dr. Hal M. Davison on the Committee on Nomenclature. Drs. Feinberg and Wittich had prepared suggestions for the Constitution and By Laws, which

—Courtesy of Werner Beyeler Co., Zurich

Nine members of the Executive Committee of the IAA following the closing dinner September 28 at Congress Hall, Zurich:

(Left to right)

1. Dr. Samuel M. Feinberg, President-elect, IAA; Professor of Medicine, Chief of Section of Allergy and Director of Allergy Research Laboratory, Northwestern University Medical School, Chicago.

2. Dr. Fred W. Wittich, President, IAA; Secretary-Treasurer, American College of Allergists, Minneapolis.

3. Prof. Dr. Charles W. Loeffler, President of the Congress; Member-at-Large, Executive Committee, IAA; President, Swedish Allergy Society; Kantonsspital, Medizinische Klinik, Zurich.

4. Dr. Egon Bruun, Member-at-large, Executive Committee, IAA; Chief of Allergy in Denmark, Copenhagen.

5. Prof. Arthur S. Grumbach, Treasurer, IAA; Institute of Hygiene, Zurich.

6. Dr. Francis M. Rackemann, Member-at-large, Executive Committee, IAA; clinical allergy, Boston.

7. Dr. Bernard N. Halpern, Secretary-General, IAA; Director of Research, National Center for Scientific Research, Paris.

8. Dr. D. A. Williams, Third Vice President, IAA; President, British Allergy Society; President, British Association of Allergists; Asthma and Allergy Research Unit, St. David's Hospital, Cardiff, Wales.

9. Dr. Ulysses Fabiano Alves, Jr., First Vice President, IAA, Buenos Aires.

Other members of the Executive Committee not shown are Prof. Pasteur Vallery-Radot, Second Vice President, IAA, Pasteur Institute, Paris; Dr. Ethan Allan Brown, Member-at-large, Executive Committee, IAA, Lecturer in Allergy, Tufts College Medical School, Physician-in-Chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston; and Dr. Mario Salazar-Mallen, Member-at-large, Executive Committee, IAA, Chief of Department of Allergy and Bacteriology, General Hospital, Chief of the Laboratory of Immunology (Institute of Cardiology), Mexico City.

were further elaborated by the Committee as a whole and then adopted by the voting representatives. We believe that this Constitution and By Laws will serve in the future as a model of democratic procedure and international co-operation.

The name of our association is now The International Association of Allergology. Societies which have approved and signed the new statutes are the American Academy of Allergy, the American College of Allergists, the American Society of Ophthalmologic and Otolaryngologic Allergy, the Argentine Association of Allergy and Immunology, the Argentine Society of Allergy, the Section on Allergy of Australia, the Belgium Society of Allergy, the Brazilian Society of Allergy, the British Association of Allergists, the Canadian Academy of Allergy, the Chilean Society of Allergy, the Cuban Society of Allergy, the Danish Society for Allergological Research, the Dutch Society of Allergy, the Spanish Society of Allergy, the Finnish Society of Allergy, the Israel Society of Allergy, the Italian Society for the Study of Allergy, the Mexican Society of Allergists, the Netherlands Society of Allergy, the Peruvian Society of Allergy, the Portuguese Society of Allergy, the South-African Allergy Society, the Swedish Association of Allergists, the Swiss Society of Allergy, and the Uruguayan Society of Allergy. The following societies were originally affiliated with the organization of the International Association of Allergists but had no representative present at this Congress: The Colombian Society of Allergy, the Hungarian Society of Allergists, and the Japanese Society for Allergy. The French Society of Allergy, while not among the original organizers, has subsequently affiliated with the IAA.

While membership in the association will be by national allergy societies, provision has been made for membership of individuals from countries where no national societies have been formed. Members of national societies automatically become members of the IAA.

Each national society elects one representative to the House of Delegates for a term of four years. The officers of the IAA, seven in number, are:

President.....Fred W. Wittich, U. S. A.
President-elect.....Samuel M. Feinberg, U. S. A.
First Vice President.....Ulysses Fabiano Alves, Jr., Brazil
Second Vice President.....Pasteur Vallery-Radot, France
Third Vice President.....David A. Williams, England
Secretary-General.....Bernard N. Halpern, France
Treasurer.....Arthur S. Grumbach, Switzerland

Members-at-large
on Executive Committee—Charles W. Loeffler, Switzerland, *Chairman*

Egon Bruun, Denmark
Ethan Allan Brown, U. S. A.
Francis M. Rackemann, U. S. A.
Mario Salazar-Mallen, Mexico

The House of Delegates forms the ruling body for the association, but the usual business between sessions, to be held every four years, will be conducted by an Executive Committee of twelve members including the seven officers, the immediate past president, and four members at large elected by the House of Delegates. The Nominating Committee consists of twelve delegates, three from Central and South America, three from

Europe, three from North America, and three at large. They nominate the officers and the four other members of the Executive Committee, but further nominations may be made by any delegate at the regular meetings of the House of Delegates. Election of the above officials is by a majority vote of the House of Delegates in regular meetings. The Executive Committee and the Finance Committee fix the dues to be paid by national societies and by individual members from countries where no national society exists. The Committee on Nomenclature, recognizing the importance of establishing proper definitions acceptable to all nationalities, elected a small committee with an Executive Secretary to act as a clearing house for the work during the next four years. Contacts with all members of the Committee will continue by correspondence, and the report will be made at the next meeting. The Committee unanimously selected Dr. D. Duchaine of Brussels, Belgium, for the post of Executive Secretary.

Since no official journal has been established for the International Association of Allergology, résumés of the papers presented at this Congress will be published in a "Proceedings" printed by S. Karger, Switzerland. Much news about the Congress will appear in the forthcoming issue of the *International Archives of Allergy and Applied Immunology*, which is now the official organ for publishing the proceedings of many national allergy societies.

Brazil had the largest representation from the greatest distance. Their invitation to have the Second International Congress in Brazil was unanimously accepted. No location could be more appropriate, not only for its beautiful scenery and attractions but for its centers of learning. We can be sure that the local committee and the Brazilian Government will extend their hospitality to the utmost. The Second Congress will be held in the fall of the year, which is ideal. Those of us who were present in Zurich look forward to the reunion with those we met there and urge others in our societies to plan to be present at our next meeting. The future of the International Association of Allergology lies in the cordial friendship of individuals interested in the advancement and the dissemination of our knowledge of allergy and its basic principles throughout the world.

—Hal M. Davison, M.D.

SPEECH OF PRESENTATION

By Fred W. Wittich, M.D.

On the Occasion of Conferring Honorary Degrees

The accomplishments of world renowned scientists continue throughout their existence and survive as milestones of progress for future generations.

Today, the International Association of Allergists at its first International Congress has the great distinction of pausing at one of the milestones of these honored men to pay tribute. It is needless to cite their fundamental scientific contributions upon which our knowledge of the diseases of hypersensitiveness is based, as they are familiar to all of you. Their endeavors were no doubt inspired by previous pioneers who now have passed beyond.

This first International Congress representing thirty-nine national socie-

—Courtesy of Werner Beyeler Co., Zurich

Dr. Fred W. Wittich, President, IAA; Chairman, Executive Committee, IAA; Secretary-Treasurer, American College of Allergists, Minneapolis, conferring honorary fellowship degrees upon those elected by the Executive Committee of the International Association of Allergists (now also elected honorary members of the International Association of Allergology) at the opening ceremony, September 23, Congress Hall, Zurich.

ties would be sadly negligent not to show its appreciation and respect for some of those who have carried the torch for us.

The officers of this Association, therefore, take great pride and pleasure in bestowing Honorary Fellowship upon the following:

Prof. Dr. Arthur F. Coca	New Jersey
Sir Henry Dale	London
Prof. Dr. Robert Doerr	Basel
Prof. Dr. Cesare Frugoni	Rome
Prof. Dr. M. Heidelberger	New York
Prof. Dr. Paul Karrer	Zurich
Prof. Dr. R. Otto	Frankfurt
Prof. Paul Portier	Paris
Prof. Dr. Robert Rössle	Berlin
Prof. Dr. Bela Schick	New York

PROCEEDINGS OF FIRST INTERNATIONAL CONGRESS ON ALLERGY

It is hoped that the *Proceedings of the First International Congress on Allergy*, a full report of the papers presented at the Zurich meeting, September 23-29, 1951, will be ready to go to the printers about May 1.

The Association of American Physicians and Surgeons, Inc.

The Association of American Physicians and Surgeons, Inc., held its annual meeting in Indianapolis, Indiana, October 4, 5 and 6. C. E. Umphrey, M.D., president, Michigan State Medical Society, Detroit, presented a paper on "Political Vandalism versus the Rights of the Individual." The Honorable J. Bracken Lee, Governor of Utah, spoke on "Freedom in Government." Lawrence Shinabery, M.D., president, AAPS, spoke on its past, present, and future. The Honorable John L. McClellan, U. S. Senator from Arkansas, gave a very stimulating address on "National Affairs," and George N. Craig, past national commander of the American Legion, Indianapolis, presented "For This We Fight."

Some facts brought out are startling. The effect of our tremendous national debt, with increases of taxes and inflation, upon our insurance was shown. A $10,000 policy purchased in 1940 has shrunk in protective value by at least 50 per cent. A typical life insurance holder today should have a planned estate of about $150,000. In five years it will be probably be $200,000 to offset a twenty-five-cent dollar.

Our federal government is in business where the huge losses sustained must be borne by the already overburdened taxpayer. The post office loses 500 millions each year. Government-controlled power industries lose 450 millions a year, while those under the aegis of private enterprise pay taxes in a like amount. In spite of these facts our government, which now controls 200 power plants and dams, is planning on building 500 more. Our government is already in the banking business, financing endeavors from race tracks to soda fountains. It has built up a tremendous insurance business for war veterans and their dependents. It is in the peanut, cotton, beans, turpentine, turkey, and wool business. It buries thousands of tons of eggs underground to make you pay more. It owns at least two railroads, several barge lines, and many merchant marine ships. It smelts metals, refines sugar, and proposes to build steel plants. It operates scores of hospitals, hires doctors, dentists, oculists, and surgeons. It is in the business of fixing wages, pensions, prices, profits, interest rates, and dividends.

The first appropriation to a federal bureau in 1912 was less than $22,000. Now, more than $1,200 is spent annually by the federal government for every family of four, an increase of 4,038 per cent. Each family's share of the federal debt has jumped from $50 to between $7,000 and $8,000—an increase of over 14,000 per cent! According to Secretary of the Treasury Snyder we will spend seventy-five billions this year. More recently that estimate has been increased by twenty-five billions. With a federal revenue of fifty-one billions, our yearly deficit will be about fifty billions a year. Who is going to be happy to have our financial structure totter and fall?

The AAPS sends out an average of twenty-five alert Legislative Bulletins per year to key medical leaders throughout the nation, including the presidents and secretaries of the state medical associations. These Bulletins are not used as a directory of all legislation which deals with health problems but are used only for those proposals having current consideration.

either by Congressional Committee or the whole of Congress and which require immediate grass roots action.

Another important service is the AAPS News Letter, printed and distributed each month to the entire membership, state medical societies, medical leaders, and leaders in allied fields. The News Letter has gained increased acceptance each year as one of the better mediums for keeping physicians accurately and quickly informed on current happenings in medical economics, public relations, and legislation.

Since 1947 AAPS has conducted a successful essay contest and each year has awarded $1675 in cash prizes to high school students writing the best essays on "Why the Private Practice of Medicine Furnishes this Country with the Finest Medical Care."

The AAPS stands for nonparticipation of ethical physicians in any scheme for the distribution of medical care which would deprive the people of the highest quality of medical service. The plan of nonparticipation is not a "strike." A "strike" means withdrawal of services, and no AAPS member—no physician—proposes a withdrawal of service from patients. The plan is simple in design and is legal. It is proposed action of morality by physicians to protect the people from inferior medical care. AAPS proposes merely that physicians exercise their constitutional right not to participate in schemes which are contrary to the public interest. Every socialized medicine bill introduced into Congress has recognized this constitutional right by stating: "Physicians are free to participate (in the socialized medicine program) full time, part time, or *not at all.*" Nonparticipation has succeeded in British Columbia since 1936, in San Francisco since 1947, and in the Union of South Africa for the past several years.

Medicine can become socialized through the expansion of the Public Health Service, legislation for which (S-445) has been passed by the Senate and is now dormant in a committee of the House. It is no secret that the socialistic planners hope to use the expanded Public Health Service as a means to establish public medical care stations where the people would be required to receive medical care from government-paid doctors. Legislation on federal aid to medical education is reaching a critical point, and the American Legion support of this legislation very well could become the decisive factor to socialize medical and nursing education. By a ruling of the Supreme Court, federal-grants-in-aid programs are subject to control by the federal government.

More than 60 per cent of the patients in veterans' hospitals are being treated for nonservice disabilities. All that the veteran needs to do to meet the requirements for admission to a veterans' hospital is to declare that he is unable to pay for medical care. Thus private practice is slowly being wiped out by government treatment for nonservice connected disabilities. It is the duty of every physician to write to his Congressman, as this is the most effective way of combatting this creeping tendency toward socialized medicine.

In view of the continuing rapid trend towards socialized medicine, it was thought to be opportune to present this information about the AAPS and the wonderful work they are doing for freedom in the practice of medicine.

Progress in Allergy

HAY FEVER

A Review of the Literature of 1950

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Foreword

Each year the writers of this review look forward to appraising the world's literature with the hope that we may glean from it something of such sensational importance that a headlight of progress can be reported.

We predicted in our past reviews that the antihistamines would not explain or control all of the factors involved in pollinosis. We are now in the midst of the early evaluation of the adrenocorticotropic hormones. Much of the noted effects of ACTH and Cortisone as they affect Hay Fever will be reported in the review. Some interesting facts of enzyme systems affecting immunological and allergic reactions are being reported. Again we wish to reiterate that when the final chapters of allergy are written, they will involve each individual cell affected by complex immunochemical, neural, and physiologic factors, and their relation to individual shock organs.

IMMUNOCHEMISTRY

A large number of articles appeared this year with some relationship to hay fever, but a large portion of these articles dealt with specific relationships to the general immunologic concepts of allergy.

Rostenberg and Brunner,[171] in an excellent paper, discuss the theories of antibody formation. Their remarks are worthwhile reading.

Rocha e Silva[168] discussed the role played by leukocytes and platelets in anaphylactic and peptone shock.

Sheldon, Lovell and Mathews[185] review the subject of the immunologic aspects of allergy.

Schmidt[181] discusses his explanation of the allergic concept.

Jimenez Diaz and Arjona[48] report on the general subject of allergic antibodies. These authors in conjunction with Ales and Segovia[49] report on the precipitin reaction in the diagnosis of allergic patients.

An interesting report on the use of antigen tracers by Dixon and Warren,[50] discusses the site of anaphylactic shock in guinea pigs.

Traina[203] reported on his studies on anaphylactic shock. Vitamin B_{12} may act as an anaphylactic agent in protecting guinea pigs previously sensitized to horse serum.

Sympathin from spleen extracts may exert antianaphylactic action. This observation was made by Farrerons and Zauner Gutmann.[88]

In an editorial in *The Journal AMA*, the plasma cell as the key to allergy is discussed; also a survey of the literature.

Peters[152] discussed strange ways in which the allergic reaction is altered.

Loveless,[120] using several methods for the preparation of antigens from low ragweed pollens, found two specific substances which dialyze through cellophane, and at least four others which are retained by the membrane. She used the Nielsen-Kirkwood apparatus at first, and then the Tiselius procedure for final refractionation.

Campbell, Cann and Friedman[28] reported their immunologic studies on reaginic

serum fractions obtained by the electrophoresis convection techniques. Their results indicate that reagins in multiple sensitivities tend to be spread over a wider range of serum protein than those present in single sensitivities, which tended to concentrate in the beta globulin fraction. The other antibodies were more closely associated with the gamma fraction.

Asboe-Hansen[93] reported on the use of hyaluronidase, employing allergens as indicators. The intracutaneous as well as the scratch method was employed. Both types of local reactions were spread, whereas hyaluronidase pretreatment of the test site did not result in a spreading effect in the patch test reaction in sensitive individuals.

BOTANY AND POLLEN SURVEYS

From different parts of the world and different parts of the United States come reports on the results of pollen studies and surveys.

Gutmann[87] reports again from Palestine. He notes that by close observation there are several pollen seasons. He also notes new weeds heretofore not reported, namely, those causing fall symptoms; when the specific pollens were used, the result of therapy improved.

Burtness[27] reports on a two-year study from Santa Barbara, California. He found that the most important pollens were Quercus, Pinus and Cypressus. The most important fungus was Hormodendrum.

Wiley and Tarzwell[214] reported their findings before the Northwestern States Weed Control Conference on their ragweed pollen studies in the Cincinnati area during 1941. They discussed the various factors which affect the pollen count.

Wiseman, Siegal, Glazer, Chait and Walzer[216] report their results of ragweed pollen studies during 1948-1949 in the New York metropolitan area. Factors dealing with maximum pollination, wind direction, and other meteorologic conditions were evaluated.

M. Salazar Mallen[175] discussed the pollinosis problem in Mexico. Pollinosis accounts for approximately 23 to 31 per cent of all allergies seen by the author. Pollens noted were Bermuda grass, ash, short ragweed, Lesinosis, and Helianthus.

Gilbert[81] studied the variations between volumetric and gravity slide tests for airborne pollens. From his studies, for all intents and purposes, the Durham method and conversion factors still remain valid.

Other reports on pollen counting are the reports of Bubert and Goldsmith,[26] the pollen counting guide of Credille,[44] and the excellent report of Durham and his collaborators for the pollen survey committee of the American Academy of Allergy.

FUNGI

Sherman's[187] excellent editorial in the *Journal of Allergy* in regard to the present status of "Mold as Allergens" sums up our problem. There is no doubt that molds act as allergens and give excellent skin tests. The antigenic relationship between various species and genera is still lacking. It is evident from the literature that there is a difference in the molds recovered from outdoors, as compared with those recovered from indoors. Seasonal variations have also been noted by many, as well as the effects of wind and other meteorological conditions.

Much can be said about the efforts of Harris[94] and associates who are on the mold survey committee of the Research Council of the American Academy of Allergy. From their combined efforts we will finally know what is happening to the mold situation in the United States.

Flensborg and Samsoe-Jensen[73] report their findings on mold spore counts in Copenhagen. They used the Petri dish technique described by Feinberg and Bernstein. They noted a marked seasonal variation and a close relationship between

humidity and temperature for Hormodendron, which proved the most important mold in Copenhagen. The four common outdoor molds were Alternaria, Hormodendrum, Pullularia, and Penicillium. Indoors, Penicillium was most important, as well as Aspergillus and Hormodendrum.

Kalb[107] points out that molds cause trouble after the fall pollen season. He further notes other sites of mold growth such as toys, pillows, draperies, et cetera.

Wittich[218] points out that rusts, smuts and mold may contaminate the air, and that chemicals used in manufacturing plants and mills can act as nonspecific irritants.

Alemany-Vall,[3] from France, notes that in 40 per cent of the cases of allergic rhinitis and asthma, Hormodendrum, Alternaria, Aspergillus, Mucor, and Rhizopus were recovered from the environment. In 40 per cent of another group, Penicillium was noted, and in the remaining 20 per cent other fungi were noted.

Wallace et al,[210] in an intensive mold survey of air and dust from several sites in Lexington, Kentucky, reported that Penicillium and Aspergillus were the most common mold genera in both summer and winter. They also note marked variations in types of mold from different places in the same home. This points out the importance of making mold determinations at the home and the immediate surroundings.

In the Queries and Minor Notes[158] of J.A.M.A., a note about molds in home furnishings is reported.

Heise and Heise[97] wrote that a high lapse rate is responsible for the vertical disseminations of pollen and mold spores. A negative lapse rate and particularly a temperature inversion is responsible for maintaining a high concentration of allergenic particles near the ground.

Piekarski[155] reported on the role of fungi in patients with bronchial asthma and anthracosis. Penicillium, Zaleskii, and *Stysanus stemonitis* flourish in anthracite coal mines. Very little could be attributed to the long duration of work in the mines in relation to the development of skin sensitivity or clinical symptomatology.

Christensen et al[39] report on the intramural dissemination of spores of Hormodendrum resinae when liberated on the first floor of a four-story building. In a few minutes, when the doors were open, the spores were recovered from the second to the fourth floors.

Morrow and Wheeler[141] in their studies on the relationship of fungi in aerobiological populations, report the effect of the Tillandsia species (ball and Spanish moss), as a source and substrate for the growth of fungi in large numbers.

STANDARDIZATION

Very little has been added to the subject to help clarify and simplify the methods used in past years. Until purer or single antigens can be prepared, the old method of a combination of biologic assay and chemical evaluations on a basis of protein and/or total nitrogen, remains our best method.

Rimington and Maunsell[167] made a very intensive study on the preparation and standardization of dust. This is a definite contribution to this year's literature. Their method of preparation does not differ much from that reported by Boatner, Efron and Dorfman. Primarily, the method of Rimington and Maunsell is an alkaline aqueous extract, neutralized and absorbed with benzoic acid, precipitated with acetone at 25 to 80 per cent followed by evaporation of the acetone. This leaves a crude antigen containing 20 to 30 per cent carbohydrate, 2 to 3 per cent nitrogen, and 35 to 50 per cent ash. Further purification is obtained by redissolving in water and dialyzing against 2 per cent citric acid followed by reprecipitation with 25 per cent and 75 per cent carbohydrate in the form of galactose, 5 to 7 per cent nitrogen, and 1 to 2 per cent ash.

From their studies they conclude that biological activity is due to the complex polypeptide complex.

Electrophoretic examination of the antigen showed two constituents: one colorless and nearly immobile, and the other a brownish pigment which contained the migrating fraction. Both contained biologic activity.

The material must contain some irritating substances, because in dilutions of 10^5 there was a 4 per cent reaction in nonallergics. The allergics reacted in dilutions between 10^5 and 10^8. The material is relatively heat stable—capable of producing dust reagins in dust-sensitive cases.

Scherago, Berkowitz, Reitman, and Hasson,[178,179] in a series of papers on this particular subject, revealed some very interesting facts. The subject of dust antigen is still open and standardization has not been settled.

DIAGNOSIS

Peshkin's[151] "Critical Evaluation of Diagnostic Tests for Sensitization in Infancy and Childhood" is one of the best articles on this subject we have ever reviewed. It is advised that everyone interested in skin tests should read this comprehensive though mooted article.

Many methods of skin testing have been suggested in the past. Morse[142] describes a method whereby he applies multiple antigens to the back and then uses electrophoresis. He applies as many as sixty-six substances. In spite of many strongly positive reactions, constitutional reactions have never been observed.

Sherman and Feldman[186] describe their intramucosal ophthalmic test. The test substance is applied just below the ocular or bulbar conjunctiva. The reaction develops very rapidly. Threshold reaction revealed that the intramucosal response is at least ten times greater than the intracutaneous test, and at least 100 times more sensitive than the conjunctival test using the drop method. This test is not suggested for general use—only on those where the skin tests are negative. It is not recommended as a routine diagnostic procedure.

Shulman[189] discusses the ophthalmic test for foods. In some instances the eye test showed itself superior in detecting an allergic condition and helped avoid a false positive test. This test has been repeatedly advocated in patients with clinical allergic symptomatology and negative skin tests. Peshkin has advocated this for years.

Chait and Walzer[34] describe a method for studying allergens by applying them to the anterior portion of the nasal septum.

Blumstein[15] describes a dry pollen nasal test. Blumstein and Tuft use a similar test to evaluate pollen nasal tolerance. It was noted that prolonged or perennial pollen therapy results in a constant and significant increase in pollen tolerance.

Morrison[140] describes an instrument capable of producing painless scratches that are consistently uniform in length and depth.

Harris and Shure[95] reported a case of fatal anaphylactic shock following intradermal tests. We again reiterate that it is always safer to do scratch tests before intradermal tests are performed; in fact, we feel it mandatory.

Gaillard[78] describes an insect allergen due to the aphid. The symptoms in his cases were not explained by seasonal inhalant allergens and gave positive skin tests to the aphid extract.

Ancona and Gardner[4] discuss the use of raw foods as skin tests. This may explain many false positive and negative tests in skin testing.

Kahn[106] discusses a patient with a positive skin test to silk, and with negative pollen tests. The patient was proven clinically sensitive to pollen, and negative to silk.

Castberg and Schwartz[32] did blood studies in hay fever patients during acute allergic shock. Blood was drawn on five patients three to six minutes after

they had had an acute constitutional reaction. A fall in blood sugar, a transient leukopenia, normal sedimentation rate, no change in eosinophil count, and a slight drop in blood pressure were noted.

DRUGS

A number of drugs have been reported which have been found useful in hay fever and asthma.

Rosenman et al[170] report their studies and observations in patients with bronchial asthma on the use of Khellin, a crystalline compound obtained from the plant Ammi visnaga Lam, otherwise known as Visammin. In doses of 100-200 mg, excellent but transitory relief was obtained in nine out of twenty patients. Side effects such as nausea, vomiting, and skin eruptions were noted frequently. They report a decrease of cyanosis, an increase in exercise tolerance, and an increased sense of well-being. The patients noted a marked relief of dyspnea and wheezing. We have used Khellin on a small group of patients and cannot report the same degree of effectiveness as was reported above.

Schapiro and Sadove[177] report a favorable result with procaine hydrochloride given orally to a patient with bronchial asthma. Our results with this drug alone or in combination with cevitamic acid or as the amide in patients with hay fever and asthma have been very disappointing. Many side reactions were noted, especially gastrointestinal upsets.

Hansel[91] reported on the use of Nethaprin (Merrill), a sympathicomimetic drug. He has found it effective in the symptomatic control of asthma. He reported that untoward effects were inconspicuous. Several years ago we also had a great deal of experience with Nethaprin. The drug was effective—especially in children. However, it is not as effective as ephedrine.

Other drugs proved useful by investigators are Norisodrine sulphate administered by inhalation as a 25 per cent dust. Swartz[199] felt this to be very effective in cases of asthma. Dibenamine is reported useful in asthma by Klotz and Bernstein.[110]

Targow[200] does not believe it advisable for patients to use a nebulizer with adrenaline. However, he does not feel that patients become addicted to its use.

In past years we reported on the use of the newer sympathicomimetic drugs alone or in combination with antihistamines, sedatives, or central nervous system stimulants. In our experience ephedrine or ephedrine combinations are still among the best drugs for hay fever, and adrenaline is the drug of choice for asthma.

SPECIFIC TREATMENT

This year, investigators reporting on studies involving specific therapy have directed their attention to the use of specific fractions of pollen.

Abramson et al[1] electrophoretically purified ragweed antigens (Trifidin and Artefolin). With the help of other allergists, fifty-six patients with hay fever and asthma were treated. The size of the molecular aggregation used for therapy was in the neighborhood of 5000. There were good results in 70 per cent of the cases. It is believed that when larger doses are given, the results will improve. The results indicate that better protection is to be expected from the purer solution when larger doses are available.

Malkiel and Feinberg[122] studied the effect of delaying ragweed extract absorption on antibody production. Experiments on normal and nonallergic human volunteers disclosed that absorption was delayed approximately 3 to 1 as compared to the aqueous extract. This was measured by the presence of circulating antibodies in the volunteers. The results of this type of therapy is equivocal.

Maietta[121] reported a new technique of shortening the treatment of hay fever by simultaneously administering pollen antigen with an antihistaminic drug. Larger doses were given at frequent intervals preseasonally, with relatively few reactions.

Excellent results were obtained in fifty-nine out of sixty-five cases. Our results with this method have not been as good as those reported by the investigator.

Black and Holman[13] treated a group of 402 children suffering from respiratory allergy. They reported good results in over 50 per cent of those treated orally with pollen and dust extract. Where the oral method failed, a large number improved by the hypodermic hyposensitization method.

Chester[38] reports on his experience in the treatment of pollen-sensitive patients who were pregnant. He prescribes specific pollen therapy, using moderate doses given preseasonally. To this we ascribe wholeheartedly, because for the past twenty years we have used this type of treatment on pregnant patients, without a single mishap.

Gaillard[80] reported on his results when using an alum-precipitated pyridine pollen extract. His results are not much different from those using the usual pollen extracts.

NONSPECIFIC THERAPY

Many substances have been used in the nonspecific therapy of hay fever and allergic rhinitis. Pyromen was tried by Randolph and Rollins.[161] Pyromen is a highly refined bacterial product containing complex polysaccharides. It is believed that the adrenocorticotropic hormones are stimulated. It is effective when given orally. It may also be injected by other routes. It is usually effective in small doses of 0.5 to 10.0 gamma. Within this range the febrile response is usually lacking. Our experience with this drug is equivocal.

Castex[33] reports some interesting results with the sodium salt of p-aminosalicylic acid. He claims it to be an effective antiallergic drug.

Chaudhuri and Ray,[35] in a series of articles, report on urinary proteose. Their results indicate that urinary proteose is capable of acting as a hyposensitizing agent. They claim that the material is specific and capable of producing specific antibodies. These were not the results obtained by one of the writers of this review (M.A.K.).

Waxler and Schack[211] give an excellent discussion in the J.A.M.A. on the administration of aminophylline.

ADRENOCORTICOTROPIC HORMONE AND CORTISONE

As was to be expected, this year saw a considerable number of reports on the evaluation and study of these newer-developed hormones. The chief cause was, of course, the increase in production by the manufacturers of ACTH and cortisone, and the natural desire upon the part of the investigators to study these hormones from every possible standpoint. These included immunochemical, biological, physiopathological, histological, and therapeutic points of view. Caution in the use of these agents seemed to keynote most of the investigative studies. Their untoward effects were noted by all who studied these drugs, in practically every paper which appeared in the scientific literature. The therapeutic effects, of course, continue to highlight the scene, and the tendency definitely points to limitations in usage of ACTH and/or cortisone to those conditions in which these hormones have proven to be most effective.

Brown[19] has presented a careful study of these hormones and has thoroughly reviewed the literature up to December, 1950. He points out the general effects of ACTH injections in depressing thyroid function and basal metabolic rate, stimulation of the pancreas to insulin production with ultimate pancreatic exhaustion and frank diabetis mellitus in some, or in others a period of hypoglycemia. The same author notes the effect of ACTH or cortisone on the posterior pituitary gland with depression of gonadal function and inhibition or delay in menses; he also mentions a type of peritonitis with normal pulse rate, without fever or rigidity; inhibition of

bone marrow, lymphopenia, delay in wound-healing, and ill effects when these hormones are used in patients with active pulmonary tuberculosis are among the many side effects mentioned. Careful studies of the blood from minute, detailed examinations are reported, including the effects on electrolyte balance and water retention. Comparative results of other adrenocortical hormones are made against cortisone and ACTH in investigative studies in animals as well as in humans.

Untoward reactions produced by these hormones were noted by Derbes and Weiss,[46] who discuss the anterior pituitary gland from the physiological and histological standpoint, and note that ACTH is derived from the acidophile cells and that this process is stimulated by release of epinephrine from the adrenal medulla. These investigators also suggest a possible autonomic source as a cause for stimulation of the adrenal medulla, causing liberation of epinephrine, which stimulates the anterior pituitary and thus creates a perpetual cycle in man and animals, both normally and in disease or during stress. These observers also discuss other adrenal steroids of the glucocorticoids, mineralocorticoid, and "N" hormone types, having effects similar to but often quite different from ACTH and cortisone. They also point out the effects of ACTH and cortisone on other glands of internal secretions, causing structural and physiologic changes.

Albright noted that all or almost all patients exhibiting Cushing's syndrome have certain changes in the basophilic cells described by Crooke. Golden and associates reported deaths in two patients who had received ACTH therapy, both of whom revealed glomerulonephritis as well as morphologic changes in the anterior pituitary.

In repeating the work of Chase, Dougherty and White, DeVries[47] employed larger doses of ACTH to stimulate the adrenal cortex of rabbits previously immunized with egg albumin. All rabbits developed a marked lymphocytopenia (average loss 69 per cent). He did *not* find a rise in circulating antibody titres concomitant with maximum drop in lymphocytes, as reported by Chase, Dougherty and White. The author also noticed that twenty-four hours after the start of the experiment, the lymphocyte count had returned to the normal range, whereas the circulating antibody titres and hematocrit values were still below those of the controls.

Hammond and Novak[90] studied the question as to whether adrenal cortical hormones could induce disintegration of circulating lymphocytes. Using rabbits immunized to sheep erythrocytes, they injected adrenal cortical steroids in oil in order to study the anamnestic reaction. Lymphocytes of the appendix, thymus, and mesenteric nodes of rabbits, when injected intravenously into normal rabbits, circulate for only about thirty minutes. If this same experiment was repeated using lymphocytes obtained from the same organs of rabbits immunized against sheep erythrocytes, there was no release of antibodies under conditions of the experimental method employed. Administration of adrenal cortical steroids to normal rabbits which also received lymphocytes intravenously from rabbits immunized against sheep erythrocytes, did not induce a release of antibodies from these cells while they were circulating.

Long and Favour[119] observed striking alterations in tuberculin type allergy during treatment with ACTH and cortisone in thirty-four treated patients. They found the tuberculin reaction obliterated in thirteen, and the beta hemolytic streptococcus (B.H.S.) reactions obliterated in nineteen of the thirty-four patients studied; and in those in whom these reactions were not blocked out, there was significant alteration of the induration and erythema in one or both intradermal tests. These authors also observed normal histamine reactions in treated and untreated patients.

Harris and Harris,[96] working with rabbits and guinea pigs which had been sensitized with tubercle bacilli (B.C.G.), found that dermal reactivity to old tuberculin and to cytoplasmic particles from tubercle bacilli, as well as systemic shock produced by intraperitoneal injection of old tuberculin, could be suppressed by treat-

ment with cortisone. Skin tests again became positive four days after cessation of treatment. They also noted that cortisone did not prevent anaphylactic shock in guinea pigs sensitized with normal horse serum, nor did it exert any influence on either the appearance of the Arthus phenomenon in rabbits injected with normal horse serum or on skin test reaction to an intradermal injection of horse serum in these rabbits.

Green[83] noted that extensive tissue damage of any kind depresses metabolism generally and suggests that one should expect a depression in antibody formation. He also states that if there is no cellular proliferation in inflammatory tissue, lesions cannot appear. This, the author feels, holds true for mitosis in malignancy cells as well as for allergic tissue states. He suggests that ACTH depresses tissue proliferation.

That 17-hydroxycorticosterone (compound F, Kendall) was found to be the chief adrenal steroid in the blood of the adrenal vein was noted by Nelson[146] and his co-workers. Using the technique of Vogt and their own method for quantitative estimation of adrenal steroids, they observed a marked increase in secretion of compound F when ACTH was administered.

Sprague[196] and his group made a series of observations on the physiologic effects of ACTH and cortisone and noted a similarity in results obtained from both of these hormones. Cortisone (in animals) maintained life of an adrenalectomized animal; increased the resistance in the latter against various forms of stress; affected protein and carbohydrate metabolism, hyperglycemia, destruction of lymphocytes and eosinophils; and increased antihyaluronidase activity, among many other observations. Since ACTH has the ability to stimulate the adrenal cortices to produce steroid hormones, some closely allied to cortisone, it therefore produces an effect similar to that of cortisone. These authors carefully studied the effect of ACTH and cortisone in certain diseases closely allied to allergy and noted the clinical benefits as well as side effects of these hormones, and also made metabolic studies relating to changes in blood chemistry and in electrolytes. (This was a well-prepared study of the metabolic and mineral changes in blood and urine in patients treated with ACTH and cortisone.)

Friedlaender and Friedlaender[77] observed the effect of ACTH on histamine intoxication in guinea pigs and noted no change before or after a single dose of pituitary adrenocorticotropic hormone. Similarly, guinea pigs sensitized to horse serum, who received ACTH four hours prior to a shocking dose of horse serum, developed anaphylactic reactions comparable to the control animals who received no prior treatment with ACTH. They conclude that the administration of ACTH does not affect antigen-antibody union *in vivo*, nor does it prevent liberation of histamine resulting from such union.

Zeller et al[222] studied adrenocorticotropic hormone on two hay fever patients who were tested with thirty-six allergens. Two hours later 0.02 ml of 1:500 ragweed solution was injected intradermally, and twenty-five minutes later a diamond-shaped area of skin, including the wheal, was removed for biopsy studies They found that scratch and intradermal tests were unaltered by ACTH therapy. Also, gross and histologic studies of passive transfer sites were not influenced by ACTH therapy. They did note a striking diminution in eosinophils in ragweed wheals in treated hay fever patients, in parallel with the blood. They comment that many investigators have shown that histamine antagonists inhibit allergic wheals, which adrenocorticotropic hormone does not do, thus suggesting an alteration in the hypersensitive state of the shock organ without influencing the skin effects by ACTH.

Randolph and Rollins[159] reported on their studies with ACTH therapy on thirteen patients suffering from hay fever and bronchial asthma, the latter being mostly of the perennial type who would qualify as "intrinsic asthmatics." They

noted that relief occurred following a single course of therapy with ACTH, lasting from one week to five months. One of their patients developed edema on two attempts to treat him; however, when the dose was lowered on a third attempt, he failed to develop any edema but also failed to show any significant improvement. They feel that prolonged treatment with ACTH is unwarranted, since short, intermittent courses yielded such good results. They noted complete to 50 per cent relief in their small series, and found that there was a changed reactivity to certain food and inhalant allergens and that some of their subjects were able to eat certain foods which had previously caused acute accentuation of their asthma.

Randolph and Rollins[160] also studied the effect of concentrated adrenal cortex extract on bronchial asthma and gastrointestinal allergy. They used this extract in propylene glycol solution, containing 250 glycogen deposition units per cc, equivalent to 25 mg of compound S and 50 mg of compound E. Intramuscular injections brought about a marked diminution in circulating eosinophils, as with pituitary ACTH, but it was less effective than the latter hormone in relieving symptoms of asthma. Concentrated adrenal cortex extract was more effective in relieving the one patient studied with gastrointestinal allergy than those with bronchial asthma. These investigators suggest that inasmuch as ACTH stimulates the production of more glucocorticoids than mineralocorticoids, and since cortisone is a naturally occurring glucocorticoid, therefore, the relief of symptoms may be the result of increasing the effect of the glucocorticoids to counterbalance that of the mineralocorticoids.

Carryer et al[30,31] studied the effects of cortisone on bronchial asthma and hay fever in three ragweed-sensitive patients. Each experienced prompt relief from symptoms, more so with bronchial asthma than with hay fever, relief occurring within three days following onset of therapy with cortisone. They felt that the improvement obtained was greater than that from hyposensitization to ragweed or following the use of antihistamines alone.

A review of the clinical observations obtained by the use of ACTH and cortisone by Hench, Kendall, Slocumb and Polley was reported by Sprague.[195] This author feels that the non-hormonal diseases which were treated are not cured by ACTH or cortisone but are favorably modified, as in leukemia. He also cautions about the unfavorable effects and notes a definite pattern into which these drugs fit therapeutically. It appears that the so-called collagen diseases and a variety of allergic or hypersensitive states are conditions in which these hormones offer the greatest therapeutic promise.

Samter[176] carefully studied the effect of ACTH on hospitalized allergic patients who were placed on a measured caloric intake. He determined the excretion of urinary 17-ketosteroids, 11-oxycorticosteroids, 11-desoxycorticosteroids, and absolute circulating eosinophil counts, and measured the respiratory capacity in percentage of breathing reserve (Tuft and Blumstein method). This investigator studied the effect of epinephrine administered in 0.8 mg dosage every four hours for four consecutive days, and of 50 mg ACTH given every four hours for four consecutive days, followed by an extensive control period. He noted an improvement in respiratory capacity in four of six patients and suggests exhaustion of the adrenal cortex by prolonged administration of epinephrine as the cause for recurring asthma during the free period following therapy. He also reviews and hypothesizes the pathogenesis of bronchial asthma, with a discussion of the mechanism involved (liberation of histamine and an "imbalance" of the autonomic nervous system).

From the literature up to December, 1950, it would appear to us that adrenocorticotropic hormone and cortisone are gradually finding their place in medicine. Certainly much has been learned of their therapeutic value as well as the dangers to be avoided. As with all new drugs, caution is urged in selecting patients in whom to use these hormones. Allergic diseases, generally, compose one of the major

spheres of expected good results, and even there one must carefully evaluate the expected benefits and weigh them against the possible ill effects. Certainly continued study is advisable, and this will undoubtedly unfold further important data during the next year.

MISCELLANEOUS

In 1950 a large number of articles appeared touching on some facet of hay fever. Among those were "Weather in Relation to Rhinitis" by Rosen;[169] "Perennial Nasal Allergy" by Montgomery;[139] "Principal Characteristics of Allergy in Children" by Cortes;[42] "Pediatric Treatment of Allergic Diseases" by Clein;[40] "Allergy in Pediatrics" by Bigler;[11] "Modern Aspects of Allergic Diseases" by Jamar,[102] and "The Therapy of Allergy in Children" by Lobo.[116]

PSYCHODYNAMICS

The relationship of psychodynamics to allergic symptoms has become more evident by the excellent papers which have appeared in the literature. The very fine study of the psychosomatic phenomena in rhinitis and asthma reported by Holmes, Treuting, Goodell and Wolff,[100] should be read by all. Other papers which will add to an understanding of the relationship of the psyche to soma in allergic individuals are those of McAuliffe,[128] Mueller, Wolff and Graham, Wolf and Wolff.[82] An entire issue of the *International Archives of Allergy and Applied Immunology* is filled with excellent articles dealing with this subject.

It is our belief that when all factors affecting the end organs responsible for allergic symptoms are understood, a better evaluation of psychodynamics will be effected. There is no doubt that the psyche plays a most important part in the degree of development of symptoms.

Other articles of importance are reported upon by Kuntz[111] who discusses the relationship of the autonomic nervous system to allergy. He states that allergy is invariably associated with a shift in the autonomic functional behavior toward predominance of the parasympathetic or cholinergic nerves. In some instances the autonomic imbalance is a factor in the etiology of the disease; in others it may be induced by the reaction of the tissues to the allergen. Inherited autonomic constitutional and emotional instabilities may be recognized as etiologic factors in many cases. The reports of Schatia and Gunnarson[86] on the role of emotions in allergic diseases are worth reading.

ANTIHISTAMINES

For the allergist one might almost say that this is the reign of antihistamines. Studies on antihistaminic substances have occupied the time and energy of investigators interested in manifestations of hypersensitivity to the extent that their writings have dominated the medical literature during the past few years. It is hoped that the summit of interest in and research on these compounds has most surely been reached. It is interesting to note in this respect that whereas in prior years most of the literature consisted of reports on individual drugs, that tendency has definitely shifted to the "general review" type of reports.

Brown and Krabek[22] presented a very complete and erudite review in this same journal. Certain of their comments are pertinent and worth repeating here. Namely, there are at present no means by which the effects of such agents can be measured with any accuracy in man. Those papers which deal with clinical evaluation concern data which cannot be reproduced excepting within very wide limits. The environment changes continuously; no two patient populations are identical; the method of clinical evaluation varies with each physician; one patient complains bitterly because of thirty minutes of symptoms, another considers himself blessed because of the same symptoms. These antihistaminic agents are inconsistent in

their action, and their effectiveness or ineffectiveness is also capricious. In summary, it appears that the antihistaminic drugs are suitable only for symtomatic relief. In general, they do not appear to affect the formation of antibodies or the antibody-antigen reaction.

A concise review of these drugs, their mode of action, dosage and administration, and side reactions was presented by Britton,[23] who concluded that they are an important addition to our symptomatic therapy of allergic disease. The best drug to use depends more upon the individual than upon its antihistaminic potency, as shown by animal experiments. He feels that these drugs are dangerous and that initial doses should be low and given at a time when the patient is not called upon to do skilled movements depending upon acts of judgment. The antihistaminic drugs are not a cure, and a search for the causes of allergy still continues. When sensitivity to extrinsic allergens can be found and proved by testing, desensitization offers an excellent chance of relief.

At a symposium on antihistaminic agents in allergy, Dragstedt[51] gave a brief analysis of what histamine and other metabolites contribute to this syndrome and concludes that the role of histamine and other metabolites in anaphylaxis has significance only to the extent that the problem of human allergy has kinship with the problem of anaphylaxis and to the extent that the agents shown to be of importance in the one case are also shown to be of importance in the other. At this same meeting, Feinberg[66] stated that the antihistaminic agents are valuable adjuncts in the symptomatic treatment of allergic manifestations. They should not and cannot replace more "basic" and more "durable" immunologic therapy of elimination and desensitization, nor should other antiallergic drugs be discarded. The antihistamines possess undesirable side reactions of which the most troublesome is sedation. The possible remote toxic effects of many drugs are still not ascertained. Because of differences in individual clinical and toxic response, it is of advantage to have available a choice of a reasonable number of drugs. Opportunity still exists for the synthesis of the ideal antihistaminic drug, which will be sufficiently potent and entirely nontoxic. The clinical evaluation of these drugs presents a complex and difficult problem and requires, at the least, the painstaking and extended effort of unbiased and astute clinical observers.

The same author[65] in commenting on five years of experience with these drugs states that their clinical effects are similar qualitatively. They are effective against moderate symptoms of seasonal hay fever; however, in severe types, in the nasal obstructive stage, in the latter part of the season, in severe seasons, and in localities of high pollen content their effectiveness may be little or none. In asthma these drugs are useless in the majority of cases. Here, desensitization with pollen extracts will prevent most of the 35 per cent of the asthma which hay fever suffers normally experience. However, in the last three or four years, as a result of high-powered publicity, the substitution of antihistamines for the more efficient asthmatic remedies and the allergic management by the physician and the patient, has resulted in actual deterioration of the management of asthma. Many limitations to the effectiveness of the antihistamines are present. They do not relieve all types of allergic manifestations. They are not effective due to the limitations of the amount of histamine which can be combated by the amount of antihistamine that can be tolerated, and also due to the fact that other than histamine effects may be present in the allergic reaction. They fail to affect all phenomena of an allergic manifestation. Their action is of short duration. One of the most important limiting factors is the toxicity of this class of drugs. Marked individual differences exist in the therapeutic and toxic responsiveness to antihistamines in general.

Commenting further on their clinical use, he[63] stated that this is based on the knowledge that hypersensitivity reactions are related to the action of histamine.

The particular drug used is judged by the clinical response and its side effects, particularly sedation.

In discussing the use of various drugs in the treatment of allergic manifestations of the nose and eyes, Feinberg[67] emphasizes that they are only adjuncts in the therapy of these conditions. Far more basic, complete and lasting is the immunologic management, which consists of elimination of the offending allergen or desensitization to it. Drugs are not a substitute for laziness or disinterest in applying oneself to the more laborious procedure of making an allergic diagnosis. The antihistamine drugs, if employed only as a short-cut to replace specific allergic management, will give poorer results; and one is derelict in his duty, which is to give the patient the best treatment available.

Loew[118] gave a concise review of the pharmacology, toxicology, and therapeutics of antihistamines. He stated that the antihistamines readily reduce the congestion of the mucous membranes—which has certainly not been the general experience of most allergists. Another statement open to criticism is that the efficiency of "hyposensitization" therapy is no greater than that readily obtained with antihistamines.

Sternberg et al,[198] utilizing histamine electrophoresis, evaluated thirteen antihistaminic drugs as to their comparative antihistaminic activity in man. Their results showed Pyribenzamine, Benadryl, Neo-Antergan and Hydrillin to be the most active as determined by this method. It was also demonstrated that the subjects varied widely in their response to the same drug.

Seyler[184] divided the various antihistaminic agents into four groups on the basis of structural formulae, and felt that an understanding of the relationship of these compounds would permit more intelligent use of them. Clinical experience has shown that patients not relieved by one of them will often receive satisfactory relief from some other one; also, that side reactions that prevent entirely the use of one may be absent or tolerated when another type is used. Loew[117] made a cogent point in reviewing the pharmacology and specificity of antihistamine drugs, saying that even though "relatively" specific, when used as research tools or diagnostic aids, due consideration must be given to a variety of pharmacological actions when experiments are planned and the findings interpreted.

Wells[213] reviewed some of his work on the competition between antihistaminic agents and histamine for the receptor cell. Ratner[162] concluded that from their mode of action, it was obvious that these drugs can act only as palliative agents and do not eliminate the basic mechanism responsible for allergic symptomatology.

Using the Dale technique on the isolated intestine and the histamine intoxication method on the intact guinea pig, Keeney[108] rated several of the more common antihistamines as to their activity. He feels that they are effective in seasonal allergic rhinitis and are best employed when combined with desensitization therapy. There is considerable individual variation of response, both as to clinical effectiveness and toxicity. Optimal results may be secured by using combinations of these compounds or changing from one to another. From Dreyer's[52] experiments it seems clear that the antihistaminic drugs do not diminish or abolish with equal ease all the various actions of histamine. They are different chemical substances which exhibit different pharmacological and clinical properties, and it is reasonable to assume that these drugs will give different results clinically; he feels that the tendency to group all of the antihistamines together is unwarranted. Meier[131] reviewed the specific sympathicolytic, sympathicomimetic, and histaminolytic effects of the aromatic imidazoline derivatives. An interesting study on the possible action of the antihistamines was performed by Farrerons.[62] Histamine determinations were made on rabbits before and after they received heavy doses of antihistamines. With the exception of four animals the histamine level remained invariable. These results led the author to conclude that the mechanism of action of these drugs is distinct from that of neutralization or destruction. A cursory review of the

actions and uses of the antihistamines was presented by Hiles.[98] Brown[20] discussed the various antihistamines with emphasis on their side reactions. On the basis of present sales for "anti-cold" treatment alone, he estimates that one can expect 17,000,000 people to suffer mild reactions and an additional 8,000,000 severe reactions. Patients taking these drugs must be warned that symptoms, varying from loss of judgment and drowsiness to fatal anemia, may result from unsupervised use.

Ratner[162] reported that a special committee on child welfare stressed the dangers to children of the new antihistamine type drugs now sold openly over the drug store counters. This committee warned that these drugs may be more toxic to children than to adults. A case is reported of a two-year-old child who ate nineteen capsules of an antihistamine drug and immediately went into convulsions expiring thirteen hours later. Another case of a sixteen-month-old child with the same results following just an adult dosage was also reported. The side effects in a child may unquestionably result in accidental death because his judgment is gone.

Spielman[194] treated seventy-three patients with various allergic conditions with Perazil, one of the later antihistamines to appear on the market. Of these, 81 per cent showed marked improvement, while 13 per cent were unimproved. The most outstanding benefits were obtained in the hay fever patients. One half of the patients were under adequate hyposensitization treatment. Toxic side effects were minimal and he felt that this drug exhibited prolonged duration of action.

Animal experiments by Feinberg[68] showed that the onset of maximal activity of this compound is delayed. Of 125 patients with hay fever, sixty-two obtained effective relief. The degree of relief and percentage of patients helped was higher in the group getting hyposensitization treatment. This compound showed a tendency toward a prolonged effect, compared with other antihistaminic drugs. The prolongation of action, however, did not reach the point anticipated by some previously reported laboratory findings.

Ehrlich and Kaplan[58] found that Perazil was another antihistaminic drug that compared more or less favorably with others available in so far as effectiveness and side effects are concerned; however, this drug appeared to them to have one outstanding quality to recommend its use, namely, longer duration of effect.

Cullick and Ogden[45] did a study in which Perazil was evaluated while being alternated with a placebo. The dosage varied from 50 to 100 mg daily. Twenty-seven patients with hay fever who were not receiving specific hyposensitization therapy were alternated week to week on this drug and a placebo. A statistical evaluation of the data was made and the authors concluded that Perazil, a longer-acting antihistamine, was highly significant in the reduction of the hours of severe symptoms and of all symptoms. Percentage of side reactions was low, due to the prolonged action of the drug, and less frequent administration was necessary.

Brown et al[21] treated 186 patients with Perazil in doses ranging from 12.5 to 200 mg daily. These patients had various allergic complaints, seventy-five of whom had hay fever. Reactions were mild in one and moderate in five, usually associated with doses in excess of 160 mg daily. Their results would seem to indicate that this antihistamine is long-acting and quite effective. Although there was no exact tabulation of their statistics, it was the opinion of these physicians that this preparation was the most effective of all the antihistaminic agents that they studied.

Silbert[190] evaluated Chlor-Trimeton in a total of 117 patients with a variety of allergic conditions. In 58 cases of hay fever, 84 per cent experienced complete relief, and there was a general lack of disturbing side effects. A group of 136 cases of different allergic manifestations were treated with Chlor-Trimeton by Reicher and Schwartz.[164] Ninety-five were hay fever patients and sixty-four obtained moderate to marked relief. They felt that the clinical advantage of this preparation was its potency in small doses. There was only mild toxicity, about

14 per cent side reactions, and in only one case was it necessary to discontinue the drug.

Margolin and Tislow[123] stated that a review of the literature showed a remarkable parallelism between the therapeutic indices obtained in the laboratory and the excellent clinical results obtained with Trimeton and Chlor-Trimeton. They felt that the relatively greater safety and efficacy of Chlor-Trimeton and Trimeton by comparison with other antihistamines, as indicated in the laboratory, have been borne out by numerous clinical reports. They further stated that Chlor-Trimeton is the most effective of all antihistamines. Unfortunately, they presented no real evidence to substantiate such a statement.

Gaillard[79] found that Chlor-Trimeton was a highly effective therapeutic agent, especially useful for the symptomatic relief of hay fever. It was effective in a dosage of 2 to 4 mg three times daily. He felt that it possesses an extremely low toxicity and is likely to cause no more than 3 per cent severe side reactions. Of 247 patients with seasonal hay fever, 122 of them received Chlor-Trimeton in 2 mg doses; 83 per cent showed improvement consisting of 50 to 100 per cent relief of mucus membrane inflammation and nasal discharge. One hundred fifteen patients were given 4 mg, and strangely enough the per cent of improvement was not quite as good (77.4 per cent). Total incidence of side effects was nearly 11 per cent. The greatest majority, however, were of a mild nature.

Eisenstadt[59] gave Chlor-Trimeton to eighty-six patients with respiratory allergy, with good results in sixty-six individuals; mild toxic effects occurred in three cases.

Marton[125] reported relief in 76 per cent of seventy-two cases of hay fever with the use of Diatrin. Only thirteen patients manifested side effects in a total series of 113 cases of all types studied. He concluded that the reasonably high symptomatic relief achieved and markedly low incidence of side effects makes this drug an extremely useful histamine antagonist.

Simon[192] studied the efficacy of enteric-coated antihistamines and concluded that enteric-coated Neo-Antergan, while not acting as quickly as the uncoated, appears to achieve a smoother and longer continued action. It will give as good relief from the symptoms of hay fever and hyperesthetic rhinitis in most cases, with fewer side reactions and in less quantity, than do uncoated tablets.

Miller[134] administered Neo-Antergan intravenously and intramuscularly to a group of 138 patients. It was found to be very effective in the relief of symptoms of seasonal hay fever. In seventy-two such cases about 64 per cent were improved. The intravenous method produced severe drowsiness, almost to the point of stupor. Others developed pressure symptoms in the chest, became dyspneic, and developed wheezing respirations. This method was therefore discarded in favor of the intramuscular route. The onset of relief usually occurred within ten to thirty minutes, with average duration being four to five hours. Upon discontinuance of the drug, the symptoms recurred, and were once again relieved with its re-introduction. In two patients asthma was precipitated or aggravated by the administration of Neo-Antergan. Side reactions occurred in 23 per cent of the cases. He felt that this was a valuable adjunct in the symptomatic treatment of hay fever; *it, however, will not prevent the progression of hay fever to the asthmatic state.*

Eighty-nine patients with various allergic manifestations were treated with Histadyl by Schwartz et al[182] In doses of 50 to 100 mg it afforded relief in the majority of the seasonal and nonseasonal rhinitis cases (76.6 per cent and 53.9 per cent). These results compared satisfactorily with the action of other antihistamines. Side effects (20 per cent) were less frequent than with Benadryl but about the same as with Pyribenzamine, especially as to the leading toxic symptom, namely, drowsiness.

Mothersill[145] reported on the treatment with a combination of Histadyl and

ephedrine of a group of sixty-seven hay fever patients who were sensitive to ragweed. These patients reported on 145 treatment days with Histadyl and on 147 treatment days with Histadyl and ephedrine. The two preparations were supplied in identical-appearing capsules. The incidence of satisfactory relief, ranging from fair to complete, was 87 per cent with Histadyl and 90 per cent for the combination. The incidence of side effects classified as sedation was 15 per cent with Histadyl and 9 per cent with the combination. The incidence of other side effects was 2 per cent with the antihistamine alone, and 7 per cent with the combination; most of the patients liked the combination.

From the studies of Ogden et al,[148] Pyrrolazote appeared to be a potent antihistamine which compared favorably with other similar preparations. Placebo controls showed that there was a significant difference in the amount of severe and total symptoms while on the drug. A large per cent of patients taking placebo tablets complained of side reactions; therefore, the element of suggestion must be considered in evaluating such reactions. A two-stage tablet of this drug, half dosage for immediate absorption and half delayed action, appeared to be effective.

Histamine electrophoresis in humans was felt by Perry and LeVan[150] to be a useful screening method for antihistaminic compounds. They used this method to compare the antihistaminic effects of Hydrillin and four experimental compounds, and the results were in favor of the former. Clinical effectiveness of Hydrillin was also superior to that of the four experimental compounds.

Phenergan, in the opinion of Vallery-Radot and Halpern,[206] gave the best results in cases of urticaria and allergic rhinitis. The experimental studies of Halpern[89] prove that the action of all the antihistamine antagonists is chiefly attributable to the influence on capillary permeability. If true, this would explain their efficacy in conditions such as hay fever and urticaria.

A halogenated tripelennamine (Pyribenzamine) that was selected by the synthesizing laboratory as a very promising drug was investigated by Feinberg.[64] In most cases of the animal experiments, the indicated potency was one to four times that of Pyribenzamine. This compound, clinically, was about as effective as Pyribenzamine in the relief of allergic manifestations. Side action compared favorably with most antihistaminic drugs. Toladryl, a derivative of diphenhydramine, was studied by McGavack et al,[129] who reported 85 per cent of seasonal hay fever cases getting some degree of relief. Therapeutically effective dosage varied from 25 mg to 300 mg daily. The over-all incidence of side effects was 15.8 per cent in 222 subjects; they found no reactions if the dose was less than 100 mg daily.

Wilken-Jensen[215] used Paradryl in various allergic manifestations and felt that the effect was excellent. In all, sixty-three patients were given the drug and only in two cases were side effects observed:

Rubitsky et al[174] suggest hepatic inactivation as a possible explanation for the variability of oral antihistamic therapy. In three asthmatic patients orally administered Pyribenzamines and/or Benadryl were ineffective in preventing histamine-induced dyspnea and bronchospasm. In these same patients, however, the same drugs were quite effective after rectal, intravenous, or aerosol administration. They suggested that these other modes of administration might be employed in those patients with hay fever or asthma who do not respond to the oral route of administration.

Mayer[127] gave the results of various experiments on the influence of antihistamines upon experimental sensitization, and presented a tentative answer on how the pharmacologic spectrum of these drugs accounts for their antiallergic activity. It was his opinion that Pyribenzamine acts by nullification of histamine effects. However, other pharmacologic actions are probably responsible for the activity of this drug in certain forms of allergic manifestations not connected with histamine.

Carryer and Code[29] found that the presence of Pyribenzamine did not affect

the *in vitro* liberation of histamine during the hemolytic reaction in rabbit blood.

The technique of combining the simultaneous administration of large doses of pollen antigen and an antihistaminic substance (Thephorin) resulted, according to Maietta,[121] in a significant shortening of the treatment course. It was also his opinion that this procedure rendered more uniformly effective results. This technique was used in treating sixty-five ragweed-sensitive patients, fifty-nine of whom had excellent results, five good, and one fair.

Hubbard and Berger[101] presented data on the administration of Thephorin, Trimeton, and the two drugs in combination for a period of from one to three weeks each, to 200 patients with ragweed hay fever. The incidence and degree of symptomatic relief was significantly greater with the combined drugs than with either administered separately. The incidence of side reactions with the combined preparation was the same as that observed with Thephorin but greater than that observed with Trimeton, although the number of severe reactions observed with the combination was no greater than that observed with Trimeton, and significantly less than that observed with Thephorin. Thirty-seven and one-half per cent of the patients preferred the combination, 30 per cent preferred Trimeton, 25 per cent preferred Thephorin, and 7.5 per cent found all about equally useful. They concluded that there is a definite though incomplete antagonism in the side reaction of the two drugs.

The reports that follow deal with some major untoward effects encountered with the use of the antihistamines. Yapaloter and Rockwell[220] write of an eighteen-year-old youth who was hospitalized with the presumptive diagnosis of schizophrenia. There had been no evidence of psychotic abnormality prior to the present hospitalization. For a two-month period of time this patient had been taking 25 mg of Trimeton three times daily. After he was hospitalized, there was gradual improvement, with the symptoms beginning to disappear on the eighth hospital day. Subsequent experimental administration of Trimeton after discharge produced significant electro-encephalographic changes within three days. Trimeton again appeared implicated in the cases reported by Waldman and Pelner. A four-year-old boy and a twenty-two-year-old woman, each of whom had received large doses of Trimeton, developed signs and symptoms of toxic psychosis. Recovery occurred in both cases. In the second case Neostigmine was apparently successfully employed as an atropine-like antidote for the antihistamine.

An unusual reaction following the use of Pyribenzamine (estimated dosage 1350 mg in forty-eight hours) was reported by Towers and Giuffia.[202] Initial complaints were inability to breathe, pain in the anterior chest radiating to the neck, followed by a period of deep cyanosis, rigidity of the entire body, and inaudible heart sounds; subsequently she became irrational and unco-operative. Within twenty-four hours her mental status was normal.

Sherman and Cooke[188] saw a contact dermatitis from the use of Antistine eye-drops and a dermatitis medicamentosa apparently due to Pyribenzamine taken orally. Mosko and Peterson[144] also saw a case of severe contact dermatitis following the use of an Antistine ophthalmic solution. The dermatitis subsided following wet compresses. Patch tests with available contactant substances yielded a strongly positive patch test to Antistine after fourteen hours, with the formation of a large ulcer at the site of application. The direct intradermal skin test for Antistine was negative in regard to an immediate reaction but gave a strong positive after forty-eight hours.

A report of a fatal case of Anthisan poisoning is given by Miller and Pedley;[133] a sixteen-month-old infant was playing with Anthisan; the exact number of tablets taken was unknown. Two and one-half hours later the child became unconscious, with muscular twitchings and foaming at the mouth and nose. On arrival at the

hospital one-half hour later, the child was dead; gross autopsy revealed no evidence of organic disease.

Martland and Guck[124] wrote of a nurse who had taken eighty-five 50-mg tablets of Pyribenzamine for hay fever in a period of five weeks, and developed agranulocytosis. The drug was discontinued and the patient treated with antibiotics and liver; she responded to therapy. Subsequently, a 50-mg test dose of this drug was given orally and symptoms returned. The following day three doses were given and there was a progressive lowering of the total white blood count, as evidenced by serial counts, although a leukopenia did not develop. In view of the repetition of symptoms, it was believed that further testing was inadvisable. It was their feeling that although this complication rarely occurs, periodic blood counts are warranted in those patients receiving prolonged antihistamine therapy.

Two cases of sexual impotence in males are reported by Jennes[104] following the administration of antihistaminic drugs. In both cases, Pyribenzamine caused this unusual side reaction. In addition, in the second case, Thephorin also produced sexual impotence. In both cases, the impotence cleared up with the immediate discontinuance of the drugs. The present authors observed a similar reaction in a male who had taken Histadyl, with complete disappearance of the symptoms following discontinuance of the medication.

Hilker[99] notes a case of agranulocytosis following the use of Pyribenzamine three times daily for eight weeks; no other medicaments were involved. The patient recovered following discontinuance of the drug and the use of penicillin.

REVIEW OF BOOKS

The outstanding book for this year is the late John Freeman's[233] *A Key to the Allergic Disorders.* It is a very unusual book in many ways. Freeman has given us his observations which date from the early period of specific hay fever therapy. Together with Noon, Freeman has laid much of the ground work for the present specific treatment of hay fever. This book is different from many books on this subject because of its originality. Freeman does not conform to the orthodox method of therapy when he advises "self-inoculation." It can probably be given with relative safety in England where grass pollen is the major offender, but in the U.S.A., where many other pollens come into the picture, we feel that "self-inoculation" is dangerous. He says that it took him twenty-five years to write this book, and we would recommend that anyone who is interested in this subject should read it carefully. It is a classic, and will long be remembered.

In Paul Kallos'[236] *Progress in Allergy,* which was written in collaboration with outstanding contributors, and which can be had in both English and German versions, one may find many chapters worth reading.

Books dealing with the basic and fundamental theories of allergy are those written by Abderhalden,[223] Doerr,[230] Selye,[242] Selye and Stone,[243] Vaughan,[244] and Rost.[240]

Psychosomatic medicine in relation to allergy is evidenced by the fine books of Franz Alexander,[224] Groen,[234] and Holmes et al.[235]

Books in foreign languages are noted by Cadrecha y Fernandes,[228] Naranjo et al,[238] Groen,[234] Kallos,[236], Abderhalden,[223] Doerr,[230] and Benda and Urquia.[227]

For those interested in ACTH and cortisone, the books by Mote[237] and Selye[242] are very important.

Several noteworthy books on asthma are by Bansky,[225] Benda and Urquia,[227] Groen,[234] Francis,[232] and Segal.[241]

Two excellent books on antihistamines are by Feinberg and Malkiel,[231] and by Wishnefsky.[245]

The chapter on allergy found in Conn's[229] *Current Therapy* is worth reading, and the book on food allergy by Rinkel et al[239] is worth perusal.

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CANADIAN ACADEMY OF ALLERGY

The next annual meeting of the Canadian Academy of Allergy will be held at the Banff Springs Hotel on Tuesday, June 10, 1952, prior to the meeting of the Canadian Medical Association. Any American allergists who wish to attend this meeting are cordially invited to do so. An excellent program is being arranged.

News Items

AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold two postgraduate courses in allergy the three days preceding their annual meeting, February 15, 16, 17. One course will be held at the Sherman Hotel, Chicago. On Friday, February 15, will be Techniques of Experimental Immunology as Applied to Allergy, 1:00-6:00 p.m. and 7:30-9:00 p.m. This is a symposium of immunologists and immunochemists which will outline in simple terms physical, chemical, and immunological methods and their application in the study of allergy. Topics are physical methods (electrophoresis and ultracentrifuge), quantitative precipitin techniques, complement fixation tests, Schultz-Dale technique, and tracer techniques. A round table discussion will be held from 9:00 to 10:00 p.m.

On Saturday, February 16, a Visiting Allergy Clinic will combine didactic and "bedside" teaching. Residents and attending staff of universities and hospitals in Chicago will present patients to guest lecturers for diagnostic and therapeutic comment.

Sunday, February 17, will feature a course in dermatologic allergy.

As there is an exceptional faculty, the course should be well attended.

The second postgraduate course will be Identification and Biology of Fungi and Pollen, February 15, 16, 17, at the Northwestern University Medical School, Chicago campus.

Both courses are open to physicians and technicians. The fee is $25 for the entire course or any part of it. Those interested should contact Max Samter, M.D., University of Illinois, College of Medicine, 1853 W. Polk Street, Chicago 12, Illinois.

IAA HONORARY BANQUET

On September 23, 1951, at the Kongress Haus, Zurich, an honorary banquet was held in connection with the First Congress of the International Association of Allergology. Those present were Philipp Etter, Federal Councillor, Honorary President; W. Spühler, Alderman; P. Vollenweider, Director of the Federal Health Department; Fritz Schwarz, Dean of the Faculty of Medicine, Zurich; G. Flückiger, Director of the Federal Veterinary Board; E. Diem, President of the Doctors' Association of Zurich; A. Mann, Treasurer of the Congress; F. Stüssi, Rector of the Polytechnical School; H. Streuli, Director of the Cantonal Financial Board; Bela Schick, Honorary Guest; P. Karrer, Rector of the University of Zurich; W. Biber, President of the Cantonal Doctors' Association; A. Grumbach, General Secretary of the Congress; E. Forster, President of the Swiss Doctors' Association; H. Meuli, Brigadier, Swiss Chief Army Surgeon; G. Miescher, President of the Swiss Academy of Medical Sciences; Fred W. Wittich, President, IAA; and J. Heusser, Councillor to the Government.

INTERNATIONAL ORGANIZATION FOR AEROSOLOGY

Samuel J. Prigal, M.D., calls attention to a report which recently appeared in *Science* (November 23, 1951) in which the meetings of the Italian Congress on Aerosol Therapy were reviewed. At the conclusion of the meetings it was decided to form an International Organization for Aerosology, to include all workers in the field, nonmedical as well as medical.

Doctor Prigal wishes to hear from workers in this field interested in the formation of an American society prior to the affiliation with the international group. His address is Samuel J. Prigal, M.D., 55 Park Avenue, New York 16, N. Y.

MID-SOUTH ALLERGY FORUM

The Mid-South Allergy Forum had its first meeting of the season on November 14 at the University Club of Memphis, Tennessee. Following dinner, a round table discussion was held on the use of ACTH, cortisone, and Pyromen in allergic conditions.

Officers for the coming year are Sam H. Sanders, M.D., F.A.C.A., President; and Bernard M. Zussman, M.D., F.A.C.A., Secretary.

SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association will hold its Seventh Annual Meeting at the Bon Air Hotel, Augusta, Georgia, on March 21 and 22, 1952.

NEW SUSTAINING MEMBERS

We take pleasure in announcing two new Sustaining Members of The American College of Allergists. One is Center Laboratories, 748 Sterling Place, Brooklyn 16, New York; Mr. J. George Center, Manager. The other is Allergy-Free Products, 1431 North Broadway, Springfield 1, Missouri; Mr. and Mrs. M. G. Gray, Managers. We welcome these new members into the privileges of our society, and invite all Fellows to look for their advertisements in this issue of the ANNALS and to visit their booths at our forthcoming convention.

NEWS ABOUT ACA MEMBERS

Fred W. Wittich, M.D., F.A.C.A., Minneapolis, has been appointed a member of the Editorial Board of *Folia Clinica Internacional,* published at Barcelona, Spain, under the direction of Dr. F. Arasa of Barcelona. The Committee of Publication, besides Dr. Arasa, consists of Drs. H. Bennhold, Tübingen; Gv. Bergmann, München; W. R. Hess, Zurich; B. A. Houssay, Buenos Aires; E. Kretschner, Tübingen; E. Moniz, Lisbon; and M. P. Weil, Paris. There is a large Advisory Board of scientists from all parts of the world. Although only about a year old, the *Folia Clinica Internacional* has had unprecedented development.

* * *

E. Paul Shepard, M.D., F.A.C.A., Chillicothe, Ohio, has been granted a patent for an invention which he calls "film position indicator for motion picture cameras." It provides a visible and audible signal in determining the points in the progress of the film at which the user should start and stop the photographing of scenes, thus avoiding the usual waste of film.

* * *

Fred W. Wittich, M.D., F.A.C.A., Minneapolis, was elected an Honorary Member of the Societe Francaise d'Allergie, at the Annual General Assembly held on November 20, 1951. The announcement was received from Doctor Blamoutier, Secretariat General.

* * *

Paul Kallòs, M.D., F.A.C.A. (Honorary), of Helsingborg, Sweden, has been elected Corresponding Member of the French Allergy Society.

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Nathan Schaffer, M.D., F.A.C.A., announces the removal of his office from 172 South Arlington Avenue, East Orange, New Jersey, to 98 South Munn Avenue, East Orange, New Jersey.

* * *

William Kaufman, M.D., F.A.C.A., will read a paper entitled "Psychosomatic Aspects of Food Allergy" before the American Psychosomatic Society at their annual meeting in Chicago. He will stress some aspects of food allergy which are frequently misunderstood by psychiatrists.

BOOK REVIEWS

PROGRESS IN ALLERGY (FORTSCHRITTE DER ALLERGIELEHRE) III. Edited by Paul Kallòs, M.D., Helsingborg, Sweden. 13 contributors. 572 pages, 82 figures, one colored plate, 61 tables. Price $16.25. Basel, Switzerland: S. Karger, 1952.†

This third volume of *Progress in Allergy* is larger and better than ever. It represents the authoritative contributions of men who have devoted study to a certain phase of the subject. The introduction by the editor is a brief but critical survey of the extensive literature in the field.

The first chapter, 120 pages on allergy in children, by M. Murray Peshkin, is a monograph in itself; it provides a critical evaluation of diagnostic tests for sensitivity in infancy and all the allergy syndromes; both diagnosis and treatment are complete. The chapter on bronchial asthma by Leon Unger is concise, practical, and accurate; the photographs are illustrative. The etiology, anatomy, pathology, diagnosis, and specific as well as nonspecific treatment of asthma are presented. The chapter on bronchial asthma due to food allergy is written by Albert Rowe, whose main objective in life has been to solve the problem in allergy which offers the greatest difficulties and is probably the least understood. Some parts of the chapter may be controversial, but this is probably due to the author's greater insight into the subject. As usual, his statistics are accurate and are supplemented by illustrative case reports. In the chapter on the infective factor in asthma and rhinitis, David Harley aptly points out, when discussing the aspects of bacterial-sensitization and bacterial-allergy, that the subject does not always receive from clinical allergists the consideration it deserves. In his opinion, the reasons are lack of suitable training in the basic sciences of immunology and bacteriology and the preoccupation of many allergists with routine intradermal skin tests which commonly produce false positive reactions. He believes that bacterial-sensitization, focal infection, pathogen-selective culture, and vaccine therapy must be given proper evaluation.

The one chapter in German by Von F. Wyss and W. Hadorn is on a quantitative method for estimation of the asthmatic state by measuring expiration. Vital capacity observations were made with a pneumometer designed by Hadorn, which is illustrated and also shown in diagram form. Comparisons of various pneumometers are made in minute detail, discussing the different apparatus used as well as various antiallergic medication during asthma attacks, between attacks, in emphysema, and in cardiac dyspnea.

Joseph Harkavy, who has made a life study of cardiovascular allergy, condenses into fifty pages every phase of the subject. He traces sensitization by foreign substances such as foods, pollens, sera, drugs, antibiotics, and shows how different types of bacteria may be followed in hypersensitive individuals by various degrees of hyperergic reactions in the cardiovascular system. Many physicians do not appreciate the various protean manifestations of vascular allergy.

Two chapters appear on the ergot alkaloids, one by Prof. A. Stoll of Zurich, and one on allergy, the autonomic nervous system and ergot alkaloids by E. Rothlin and R. Bircher. The latter is an excellent dissertation on the role played by the autonomic nervous system and autonomic drugs in allergy, and what results have been obtained with ergot alkaloids in allergies. There are complete tables on the pharmacodynamic properties of the ergot alkaloids and their action on the central nervous system, vasomotor center, et cetera, as well as peripheral effects, antihistaminic and

†Distributed in U.S.A. by Interscience Publishers, Inc., New York, N. Y.

antianaphylactic effects of ergot alkaloids; and the reader obtains a broader concept of the treatment of allergies. In allergies, not only histamine but also acetylcholine and adrenaline can cause hyperexcitability of autonomic effector organs. The higher autonomic, psychic, and somatic centers of regulation can influence allergic processes. Consequently, allergies can be effectively treated not only by antihistamines but also by peripheral anesthetic drugs, vagolytics, sympathicolytics, synaptic blocking agents, central sedatives, and vasoconstrictor agents, while calcium ions, by reason of their dehydrating and antianaphylactic properties, are also effective. There are over six pages of bibliography to this important chapter.

Drug allergies are succinctly condensed by a master in this field, Ethan Allan Brown. This chapter is complemented by an article on sedormid purpura by J. F. Ackroyd. Apparently continued use of this sedative is more prevalent in Europe than it is now in the United States. The author's detailed, accurate observations indicate a way to study other drugs which produce purpura. There is a striking color photograph of the result of a patch test with sedormid on a patient who had recovered from sedormid purpura. The skin which was in contact with sedormid shows numerous closely packed petechial hemorrhages.

The publishers should be complimented for their excellent photographs, paper stock, and readable print.

ALLERGY IN RELATION TO PEDIATRICS. Edited by Bret Ratner, M.D. 17 contributors. 228 pages. Price $3.75. St. Paul: Bruce Publishing Company, 1951.

This volume represents a panel discussion presented in co-operation with members of the Allergy Section of the American Academy of Pediatrics and under the auspices of the American College of Allergists at their Fifth Annual Congress. These panel discussions have a dual role: the crystallizing of knowledge of well-qualified pediatric allergists and the exchanging of ideas on controversial subjects. It is refreshing and provocative to have well-known authorities present divergent views, and the reader is credited with sufficient intelligence to draw conclusions for himself. Sixteen experts in the field of pediatric allergy participate, all of whom are connected with allergy or pediatric departments of universities and hospitals located in large cities of the United States, where they have an opportunity to observe large numbers of allergic children. The pediatrician will find this book invaluable, for it is well known that he meets allergic conditions in from 30 to 50 per cent of patients, depending upon the environment of his particular area.

Included are specialized knowledge of the fundamentals of allergy and well-organized discussions of improved methods of investigation and treatment. Bret Ratner, the editor, introduces his subject with a brief but comprehensive chapter on the genesis of allergy in infancy and childhood. T. N. Harris is well qualified for his article on the site of formation of antibodies. Ben Feingold clarifies our knowledge of infection in the allergic child and presents interesting graphs showing the dual role infection plays in allergy. Two chapters by M. Murray Peshkin and Lewis Webb Hill on critical evaluation of skin tests stress the fact that these tests are helpful but certainly not infallible. The subject of asthma is covered by William P. Buffum and Edward S. O'Keefe in two chapters detailing diagnosis, etiology, treatment, and prognosis. S. Ambrose McGee aptly discusses allergy of the intestinal tract, a subject which needs clarification. A thoughtful article by Susan Dees emphasizes the importance of neurological allergy; in addition, her bibliography is complete. J. A. Horesh presents for consideration the less commonly recognized allergic conditions in infants and children, such as mucous colitis, the celiac syndrome, cutaneous allergy, or lichen urticatus. D. W. Baruch and Hyman Miller represent a combination of expert psychiatrists and allergists in their thesis on maternal rejection. R. H. Todd calls attention to the importance of preventive allergy.

The last quarter of the book contains a group of exceptionally practical articles on the management of asthma: William C. Deamer aptly discusses environmental control; J. C. Overall evaluates the various common drugs used in the treatment of allergy; Albert V. Stoesser gives welcome prescriptions for the practical treatment of eczema in the infant and young child; and Jerome Glaser discusses every phase of office management of the allergic child.

The book is characterized by the high standards of all chapters, and the volume is extraordinarily useful because of its splendid bibliography.

IMMUNO-CATALYSIS and Related Fields of Bacteriology and Biochemistry. Second Edition. By M. G. Sevag, Ph.D., Associate Professor, Department of Bacteriology, School of Medicine, University of Pennsylvania, Philadelphia. 547 pages. Price $12.00. Springfield, Ill.: Charles C Thomas, 1951.

This book is a heroic masterpiece in the collation of all the international literature up to 1949. The relationship between enzymes and the immune process is set forth in an easily understandable manner. An explanation of, as well as a presentation of all agents involved is clearly defined, describing the physiochemical changes that take place in the tissue as the result of the antigen-antibody reaction.

The information presented in the volume should be a part of the fundamental educational requirements of the modern allergist. It serves as a very fine reference and guide to further immunological, biochemical, enzymological, and clinical research.

This work serves to emphasize again that the immunologist or allergist cannot think of the antigen-antibody reaction alone, but must have a much broader outlook and understanding to include the basic and underlying associated physiochemical changes that take place concurrently.

Unfortunately, as so often is the case in publishing any book, recent and pertinent reports are not included. This is particularly true in that the significant role of the steroids and their part in the enzyme relationship is not included. It is hoped that a future edition will include them.

UNTOWARD REACTIONS OF CORTISONE AND ACTH. By Vincent J. Derbes, M.D., and Thomas E. Weiss, M.D., Tulane University School of Medicine. 77 pages. Price $2.25. Springfield, Ill.: Charles C Thomas, 1951.

This monograph is one of the American Lecture Series in internal medicine edited by Dr. Roscoe L. Pullen, published from time to time by Charles C Thomas. This booklet is an enlargement of the material which was previously published as the special article in the *Quarterly Review of Allergy and Applied Immunology* for June, 1951. A valuable diagram and table on the mechanism of ACTH has been added. There are a comprehensive bibliography and an index. The book contains brief chapters on physiology, glands of internal secretion, electrolytes, cardiovascular system, infections, musculoskeletal system, changes in the body, central nervous system, gastrointestinal tract, and treatment.

The book is beautifully bound in genuine limp leather with rounded corners, which is most attractive. It should be at all times available to every physician who administers cortisone and ACTH.

FORMULARY FOR AEROSOL THERAPY, 2nd Ed. By Sergio Rochietta, M.D., Turin, Italy. 223 pages. Price 1500 lira. Turin: Minerva Medica, 1951.

This book, a second edition, reflects the interest in aerosol therapy in Europe, particularly Italy, where there is much enthusiasm and widespread application of this form of therapy.

At the beginning of the book there is a discussion of different types of aerosols

(liquid and solid) and the various vehicles employed in producing aerosols, with special consideration given to the value of detergents. There follows then in alphabetical order the names of various agents (antibiotics, antibacterial agents, alcohols, salts, metals, hormones, et cetera) which have been employed in aerosol form. There is no attempt at critical evaluation of the drug or the procedure employed. The formulary briefly describes the drug, its fundamental properties, indications for its use, dosage, et cetera. Specific references to the original observations, culled from American and European literature, are given. Even those who have experience with aerosol therapy will be amazed at the variety of agents which have been employed in this fashion. It is a "must" for the experimenter in this field.

INCOME OF PHYSICIANS

Physicians engaged in civilian practice in the United States—including salaried as well as independent practitioners, but excluding interns, residents, and teachers—reported an average net income of $11,058, before taxes, in 1949. This figure was revealed by the Office of Business Economics, U. S. Department of Commerce, in announcing the results of a recent extensive survey conducted jointly with the Bureau of Medical Economic Research, American Medical Association. The findings are based on a nationwide mail survey carried out in 1950 and represent the most detailed and accurate information available on physicians' incomes in recent years.

Physicians in independent practice averaged $11,858, compared with $8,272 for salaried physicians, the study shows. About four out of five physicians derived most of their medical income from independent practice, while only one out of five was salaried.

Among independent physicians, about 13 per cent made less than $3,000 net income in 1949, whereas only about 9 per cent of the salaried physicians made so little. On the other hand, about 8 per cent of the independents reported more than $25,000, but only 1 per cent of the salaried made as much.

In the twenty-year period since 1929, physicians' incomes have more than doubled, but this relative increase was practically identical with that for all earners in the general population over the same period.

Reprints of the complete article, "Income of Physicians, 1929-49," may be obtained from the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 15 cents per single copy or $11.25 per hundred copies.